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=> d his

     (FILE 'HOME' ENTERED AT 10:00:36 ON 11 JAN 2005)

     FILE 'HCAPLUS' ENTERED AT 10:00:51 ON 11 JAN 2005
                E PARKINSON/CT
                E E6+ALL
L1         13070 "PARKINSON'S DISEASE"+OLD,NT/CT
                E PARKINSONISM/CT
                E E3+ALL
L2            53 PARKINSONISM/CT (L) (HEMI OR GUAMANIAN)
                E ANTIPARKINSONIAN AGENTS/CT
                E E3+ALL
L3          3933 ANTIPARKINSONIAN AGENTS/CT
                E PARKINSON/CT
L4         24157 ?PARKIN?/BI
                E TREMOR/CT
                E E3+ALL
L5          1093 TREMOR+NT/CT
                E SHAK/CT
                E CELL DEATH/CT
                E E3+ALL
L6         83278 CELL DEATH+OLD,NT/CT
                E DEATH/CT
                E E3+ALL
L7         44708 DEATH+NT/CT (L) CELL?
                E NERVE/CT
L8          7963 L6-7 (L) NEURON?
                E NERVE/CT
                E E3+ALL
L9        170960 NERVE+OLD,NT/CT
                E AXON/CT
                E E3+ALL
L10         8301 AXON/CT
L11        14550 L9 (L) (AXON OR NEURIT?)
                E MYELIN/CT
                E E3+ALL
L12         6626 MYELIN+OLD/CT
L13         9111 L9-12 (L) (?APOPT?/BI OR DEATH? OR ?NECRO?/BI)

     FILE 'REGISTRY' ENTERED AT 10:16:49 ON 11 JAN 2005
L14           79 MLK? OR KINASE (1A) PROTEIN (1A) (MLK? OR (MULTIPLE OR MIXED) (

     FILE 'HCAPLUS' ENTERED AT 10:19:41 ON 11 JAN 2005
                E NERVE, DISEASE/CT
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L15        10477 "NERVE, DISEASE"+OLD,NT/CT (L) (DEATH OR (APOPT? OR NECRO?)/BI)
                E NERVOUS SYSTEM/CT
                E E3+ALL
L16         1017 L14 OR MLK? OR KINASE (1A) PROTEIN (1A) (MLK? OR (MULTIPLE OR M
L17        22160 NERVOUS SYSTEM+OLD,NT/CT (L) (DEATH OR DEGENERAT? OR (APOPT? OR
                E LIU Y/AU
L18         1744 E3,E13
                E LIU YA/AU
L19           70 E3,E10
L20           22 L1-5 AND L16
L21            0 L20 AND L18-19
L22            1 US20020006606/PN
L23            4 L16 AND L18-19
L24           10 L20 AND (L8 OR L13 OR L15 OR L17)
L25              QUE PY<=1998 OR AY<=1998 OR PRY<=1998 OR PD<19980514 OR AD<1998
L26            0 L24 AND L25
                 SEL AN 1-3 6 10 L24
L27            5 E1-10 AND L24
                 SEL AN L20 2-4 7-8 18
L28            6 E11-21 AND L20
L29            9 L27-28
L30           39 (L8 OR L13 OR L15 OR L17) AND L16
L31            3 L30 AND L18-19
L32            4 L23 OR L31
L33           36 L30 NOT L31

     FILE 'REGISTRY' ENTERED AT 11:08:30 ON 11 JAN 2005
                SAV TEM L14 HAR964S0/A

     FILE 'HCAPLUS' ENTERED AT 11:09:27 ON 11 JAN 2005
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SAV TEM L16 HAR964S1/A

FILE 'HCAPLUS' ENTERED AT 11:15:36 ON 11 JAN 2005
SEL AN 3-4 6 8 12 26 30-31 34 L33
L34 9 E22-39 AND L33
L35 16 L29 OR L34

=> b hcap
FILE 'HCAPLUS' ENTERED AT 11:18:02 ON 11 JAN 2005
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
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FILE COVERS 1907 - 11 Jan 2005 VOL 142 ISS 3
FILE LAST UPDATED: 10 Jan 2005 (20050110/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> d all fhitstr l32 tot

L32 ANSWER 1 OF 4 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 2001:395049 HCAPLUS
DN 135:102815
ED Entered STN: 01 Jun 2001
TI Kainate receptor activation induces **mixed lineage kinase**-mediated cellular signaling cascades via post-synaptic density protein 95
AU Savinainen, Anneli; Garcia, Elizabeth P.; Dorow, Donna; Marshall, John; **Liu, Ya Fang**
CS Department of Pharmaceutical Sciences, Northeastern University, Boston, MA, 02115, USA
SO Journal of Biological Chemistry (2001), 276(14), 11382-11386
CODEN: JBCHA3; ISSN: 0021-9258
PB American Society for Biochemistry and Molecular Biology
DT Journal
LA English
CC 2-8 (Mammalian Hormones)
AB Kainate receptor glutamate receptor 6 (GluR6) subunit-deficient and c-Jun N-terminal kinase 3 (JNK3)-null mice share similar phenotypes including resistance to kainite-induced epileptic seizures and neuronal toxicity. This suggests that JNK activation may be involved in GluR6-mediated excitotoxicity. The authors provide evidence that post-synaptic d. protein (PSD-95) links GluR6 to JNK activation by anchoring **mixed lineage kinase** (**MLK**) 2 or **MLK3**, upstream activators of JNKs, to the receptor complex. Association of **MLK2** and **MLK3** with PSD-95 in HN33 cells and rat brain prepns. is dependent upon the SH3 domain of PSD-95, and expression of GluR6 in HN33 cells activated JNKs and induced neuronal **apoptosis**. Deletion of the PSD-95-binding site of GluR6 reduced both JNK activation and neuronal toxicity. Co-expression of dominant neg. **MLK2**, **MLK3**, or mitogen-activated kinase kinase (MKK) 4 and MKK7 also significantly attenuated JNK activation and neuronal toxicity mediated by GluR6, and co-expression of PSD-95 with a deficient Src homol. 3 domain also inhibited GluR6-induced JNK activation and neuronal toxicity. The authors' results suggest that PSD-95 plays a critical role in GluR6-mediated JNK activation and excitotoxicity by anchoring **MLK** to the receptor complex.
ST kainate receptor **MLK** kinase signaling PSD95 excitotoxicity brain
IT Glutamate receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(GluR6 subunit; kainate receptor activation induction of **mixed lineage kinase**-mediated cellular signaling cascades

via PSD-95 in excitotoxicity in hippocampal neuronal cell line and brain)

IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(PSD-95 (postsynaptic d.-95); kainate receptor activation induction of **mixed lineage kinase**-mediated cellular signaling cascades via PSD-95 in excitotoxicity in hippocampal neuronal cell line and brain)

IT Protein motifs
(SH3 domain; kainate receptor activation induction of **mixed lineage kinase**-mediated cellular signaling cascades via PSD-95 in excitotoxicity in hippocampal neuronal cell line and brain)

IT **Nerve, disease**
(**death**; kainate receptor activation induction of **mixed lineage kinase**-mediated **cellular** signaling cascades via PSD-95 in excitotoxicity in hippocampal **neuronal cell** line and brain)

IT Brain
(hippocampus; kainate receptor activation induction of **mixed lineage kinase**-mediated cellular signaling cascades via PSD-95 in excitotoxicity in hippocampal neuronal cell line and brain)

IT **Apoptosis**
Brain
Signal transduction, biological
(kainate receptor activation induction of **mixed lineage kinase**-mediated **cellular** signaling cascades via PSD-95 in excitotoxicity in hippocampal **neuronal cell** line and brain)

IT Glutamate receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(kainate-binding; kainate receptor activation induction of **mixed lineage kinase**-mediated cellular signaling cascades via PSD-95 in excitotoxicity in hippocampal neuronal cell line and brain)

IT **Cell death**
(**neuron**; kainate receptor activation induction of **mixed lineage kinase**-mediated **cellular** signaling cascades via PSD-95 in excitotoxicity in hippocampal **neuronal cell** line and brain)

IT Toxicity
(neurotoxicity; kainate receptor activation induction of **mixed lineage kinase**-mediated cellular signaling cascades via PSD-95 in excitotoxicity in hippocampal neuronal cell line and brain)

IT Nerve
(toxicity; kainate receptor activation induction of **mixed lineage kinase**-mediated cellular signaling cascades via PSD-95 in excitotoxicity in hippocampal neuronal cell line and brain)

IT 192230-91-4, protein kinase MKK 4
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(4 and 7; kainate receptor activation induction of **mixed lineage kinase**-mediated cellular signaling cascades via PSD-95 in excitotoxicity in hippocampal neuronal cell line and brain)

IT **153190-46-6, mixed lineage kinase 3**
191808-07-8, mixed lineage kinase 2
291756-39-3, JNK 3 kinase
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(kainate receptor activation induction of **mixed lineage kinase**-mediated cellular signaling cascades via PSD-95 in excitotoxicity in hippocampal neuronal cell line and brain)

RE.CNT 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD
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IT **153190-46-6, mixed lineage kinase 3**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(kainate receptor activation induction of **mixed lineage kinase**-mediated cellular signaling cascades via PSD-95 in excitotoxicity in hippocampal neuronal cell line and brain)

RN 153190-46-6 HCAPLUS
CN Kinase (phosphorylating), gene PTK1 protein (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L32 ANSWER 2 OF 4 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 2001:394974 HCAPLUS
DN 135:118347
ED Entered STN: 01 Jun 2001
TI Activated JNK phosphorylates the C-terminal domain of **MLK2** that is required for **MLK2**-induced apoptosis
AU Phelan, David R.; Price, Gareth; **Liu, Ya Fang**; Dorow, Donna S.
CS Trescowthick Research Centre, Peter MacCallum Cancer Institute, Melbourne, 8006, Australia
SO Journal of Biological Chemistry (2001), 276(14), 10801-10810
CODEN: JBCHA3; ISSN: 0021-9258
PB American Society for Biochemistry and Molecular Biology
DT Journal
LA English
CC 6-1 (General Biochemistry)
AB MAP kinase signaling pathways are important mediators of cellular responses to a wide variety of stimuli. Signals pass along these pathways via kinase cascades in which three protein kinases are sequentially phosphorylated and activated, initiating a range of cellular programs including cellular proliferation, immune and inflammatory responses, and apoptosis. One such cascade involves the **mixed lineage kinase, MLK2**, signaling through MAP kinase kinase 4 and/or MAP kinase kinase 7 to the SAPK/JNK, resulting in phosphorylation of transcription factors including the oncogene, c-jun. Recently we showed that **MLK2** causes apoptosis in cultured neuronal cells and that this effect is dependent on activation of the JNK pathway. Furthermore, dominant-neg. **MLK2** blocked apoptosis induced by polyglutamine-expanded huntingtin protein, the product of the mutant Huntington's disease gene. Here we show that as well as activating the stress-signaling pathway, **MLK2** is a target for phosphorylation by activated JNK. Phosphopeptide mapping of **MLK2** proteins revealed that activated JNK2 phosphorylates multiple sites mainly within the noncatalytic C-terminal region of **MLK2** including the C-terminal 100 amino acid peptide. In addition, **MLK2** is phosphorylated in vivo within several of the same C-terminal peptides phosphorylated by JNK2 in vitro, and this phosphorylation is increased by cotransfection of JNK2 and treatment with the JNK activator, anisomycin. Cotransfection of dominant-neg. JNK kinase inhibits phosphorylation of kinase-neg. **MLK2** by anisomycin-activated JNK. Furthermore, we show that the N-terminal region of **MLK2** is sufficient to

activate JNK but that removal of the C-terminal domain abrogates the apoptotic response. Taken together, these data indicate that the apoptotic activity of **MLK2** is dependent on the C-terminal domain that is the main target for **MLK2** phosphorylation by activated JNK.

ST **MLK2** phosphorylation apoptosis JNK kinase signal transduction

IT Proteins, specific or class
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); PROC (Process)
(**MLK2**; activated JNK phosphorylates the C-terminal domain of **MLK2** that is required for **MLK2**-induced apoptosis)

IT Apoptosis
Signal transduction, biological
(activated JNK phosphorylates the C-terminal domain of **MLK2** that is required for **MLK2**-induced apoptosis)

IT Phosphorylation, biological
(protein; activated JNK phosphorylates the C-terminal domain of **MLK2** that is required for **MLK2**-induced apoptosis)

IT 155215-87-5, JNK kinase
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(activated; activated JNK phosphorylates the C-terminal domain of **MLK2** that is required for **MLK2**-induced apoptosis)

RE.CNT 51 THERE ARE 51 CITED REFERENCES AVAILABLE FOR THIS RECORD

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L32 ANSWER 3 OF 4 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 2000:445776 HCAPLUS
DN 133:175649
ED Entered STN: 04 Jul 2000
TI Activation of **MLK2**-mediated signaling cascades by polyglutamine-expanded huntingtin
AU **Liu, Ya Fang**; Dorow, Donna; Marshall, John
CS Department of Pharmaceutical Sciences, Northeastern University, Boston, MA, 02115, USA
SO Journal of Biological Chemistry (2000), 275(25), 19035-19040
CODEN: JBCHA3; ISSN: 0021-9258
PB American Society for Biochemistry and Molecular Biology
DT Journal
LA English
CC 14-10 (Mammalian Pathological Biochemistry)
AB We previously reported that expression of polyglutamine-expanded huntingtin induces apoptosis via c-Jun amino-terminal kinase (JNK) activation in HN33 cells. Extending this study, we now demonstrate a role of **mixed-lineage kinase** 2 (**MLK2**), a JNK activator, in polyglutamine-expanded huntingtin-mediated neuronal toxicity. We find that normal huntingtin interacts with **MLK2**, whereas the polyglutamine expansion interferes with this interaction. Similar to the expression of polyglutamine-expanded huntingtin, expression of **MLK2** also induces JNK activation and apoptosis in HN33 cells. Co-expression of dominant neg. **MLK2** significantly attenuates neuronal apoptosis induced by the mutated huntingtin. Furthermore, over-expression of the N terminus of normal huntingtin partially rescues the neuronal toxicity induced by **MLK2**. Our results suggest that activation of **MLK2**-mediated signaling cascades may be partially involved in neuronal death induced by polyglutamine-expanded huntingtin.
ST huntingtin polyglutamine **mixed lineage** Jun **kinase** apoptosis Huntington disease
IT **Nervous system**
(Huntington's chorea; polyglutamine-expanded huntingtin associated with activation of **mixed-lineage kinase** 2 and Jun N-terminal kinase in relation to neurotoxicity and **apoptosis** in human Huntington's disease)
IT Protein motifs
(SH3 domain; polyglutamine-expanded huntingtin associated with activation of **mixed-lineage kinase** 2 and Jun N-terminal kinase in relation to neurotoxicity and apoptosis in human Huntington's disease)
IT Brain
(hippocampus; polyglutamine-expanded huntingtin associated with activation of **mixed-lineage kinase** 2 and Jun N-terminal kinase in relation to neurotoxicity and apoptosis in human Huntington's disease)
IT Proteins, specific or class
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(huntingtin; polyglutamine-expanded huntingtin associated with activation of **mixed-lineage kinase** 2 and Jun N-terminal kinase in relation to neurotoxicity and apoptosis in human Huntington's disease)
IT Toxicity
(neurotoxicity; polyglutamine-expanded huntingtin associated with activation of **mixed-lineage kinase** 2 and Jun N-terminal kinase in relation to neurotoxicity and apoptosis in human Huntington's disease)
IT Apoptosis
Signal transduction, biological
(polyglutamine-expanded huntingtin associated with activation of **mixed-lineage kinase** 2 and Jun N-terminal kinase in relation to neurotoxicity and apoptosis in human Huntington's disease)
IT Repeat motifs (protein)
(polyglutamine; polyglutamine-expanded huntingtin associated with activation of **mixed-lineage kinase** 2 and Jun N-terminal kinase in relation to neurotoxicity and apoptosis in human Huntington's disease)
IT **Nerve**
(toxicity; polyglutamine-expanded huntingtin associated with activation of **mixed-lineage kinase** 2 and Jun N-terminal

kinase in relation to neurotoxicity and **apoptosis** in human Huntington's disease)

IT **191808-07-8, Mixed-lineage kinase** 2
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(polyglutamine-expanded huntingtin associated with activation of **mixed-lineage kinase** 2 and Jun N-terminal kinase in relation to neurotoxicity and apoptosis in human Huntington's disease)

IT 26700-71-0, Polyglutamine
RL: ADV (Adverse effect, including toxicity); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(polyglutamine-expanded huntingtin associated with activation of **mixed-lineage kinase** 2 and Jun N-terminal kinase in relation to neurotoxicity and apoptosis in human Huntington's disease)

IT 155215-87-5, JUN N-terminal kinase
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(polyglutamine-expanded huntingtin associated with activation of **mixed-lineage kinase** 2 and Jun N-terminal kinase in relation to neurotoxicity and apoptosis in human Huntington's disease)

RE.CNT 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD

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IT **191808-07-8, Mixed-lineage kinase** 2
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(polyglutamine-expanded huntingtin associated with activation of **mixed-lineage kinase** 2 and Jun N-terminal kinase in relation to neurotoxicity and apoptosis in human Huntington's disease)

RN 191808-07-8 HCAPLUS
CN Kinase (phosphorylating), protein, MLK2 (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L32 ANSWER 4 OF 4 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1999:737080 HCAPLUS
DN 131:346549
ED Entered STN: 19 Nov 1999
TI Method to identify JNK- and **MLK**-kinase inhibiting compounds for prevention of neuron **death**
IN **Liu, Ya Fang**
PA USA
SO PCT Int. Appl., 62 pp.

CODEN: PIXXD2
DT Patent
LA English
IC ICM G01N033-68
ICS G01N033-50; C12Q001-48
CC 1-11 (Pharmacology)
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9958982	A1	19991118	WO 1999-US10416	19990512
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PRAI	US 1998-85439P	P	19980514		
	US 1998-156367	A1	19980917		
	WO 1999-US10416	W	19990512		

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 9958982	ICM	G01N033-68
	ICS	G01N033-50; C12Q001-48
WO 9958982	ECLA	G01N033/50D2; G01N033/68V2
US 6811992	ECLA	G01N033/50D2; G01N033/68V2
US 2002006606	ECLA	G01N033/50D2; G01N033/68V2
US 2002058245	ECLA	G01N033/50D2; G01N033/68V2
US 2003148395	ECLA	G01N033/50D2; G01N033/68V2

AB Methods are described for identifying compds. that inhibit JNK and **MLK** kinase activity as drugs for treating a mammal susceptible to or having a neurol. condition. Methods are also disclosed for preventing neuronal cell **death** and treating neurol. conditions that involve neuronal cell **death**, particularly neurodegenerative diseases characterized by glutamine- or kainate-mediated toxicity, e.g. Huntington's disease and Alzheimer's disease.

ST JNK **MLK** kinase inhibitor screening neuroprotectant; Alzheimer drug JNK **MLK** kinase inhibitor screening; Huntington drug JNK **MLK** kinase inhibitor screening; neurodegenerative disease JNK **MLK** kinase inhibitor screening

IT Animal cell line
(HN33; JNK- and **MLK**-kinase inhibiting compound identification for prevention of neuron **death**)

IT **Nervous system**
(Huntington's chorea; JNK- and **MLK**-kinase inhibiting compound identification for prevention of neuron **death**)

IT Anti-Alzheimer's agents
Apoptosis
Drug screening
Nervous system agents
Signal transduction, biological
(JNK- and **MLK**-kinase inhibiting compound identification for prevention of **neuron death**)

IT Transcription factors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(c-jun; JNK- and **MLK**-kinase inhibiting compound identification for prevention of neuron **death**)

IT Amyloid precursor proteins
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(carboxyl-terminal fragment; JNK- and **MLK**-kinase inhibiting compound identification for prevention of neuron **death**)

IT **Nerve, disease**
(**death**; JNK- and **MLK**-kinase inhibiting compound identification for prevention of **neuron death**)

IT **Nervous system**
(**degeneration**; JNK- and **MLK**-kinase inhibiting compound identification for prevention of neuron **death**)

IT Toxins

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(excitotoxins; JNK- and **MLK**-kinase inhibiting compound identification for prevention of neuron death)
IT Mutation
(mutated protein; JNK- and **MLK**-kinase inhibiting compound identification for prevention of neuron death)
IT Proteins, general, biological studies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(mutated; JNK- and **MLK**-kinase inhibiting compound identification for prevention of neuron death)
IT Disease models
(neurodegeneration; JNK- and **MLK**-kinase inhibiting compound identification for prevention of neuron death)
IT **Cell death**
(**neuron**; JNK- and **MLK**-kinase inhibiting compound identification for prevention of **neuron** death)
IT Cytoprotective agents
(neuroprotectants; JNK- and **MLK**-kinase inhibiting compound identification for prevention of neuron death)
IT Toxins
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(neurotoxins; JNK- and **MLK**-kinase inhibiting compound identification for prevention of neuron death)
IT Proteins, specific or class
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(polyglutamine stretch-expanded huntingtin; JNK- and **MLK**-kinase inhibiting compound identification for prevention of neuron death)
IT Phosphorylation, biological
(protein; JNK- and **MLK**-kinase inhibiting compound identification for prevention of neuron death)
IT 56-86-0, L-Glutamic acid, biological studies 89-00-9, Quinolinic acid 487-79-6, Kainic acid
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(JNK- and **MLK**-kinase inhibiting compound identification for prevention of neuron death)
IT **153190-46-6**, **MLK3** kinase 155215-87-5, JNK3 kinase
191808-07-8, **MLK2** kinase 192230-91-4, SEK1 kinase
250649-03-7, **Protein kinase MLK1**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(JNK- and **MLK**-kinase inhibiting compound identification for prevention of neuron death)
IT 26700-71-0, Polyglutamine 69864-43-3, Polyglutamine
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(polyglutamine stretch-expanded huntingtin; JNK- and **MLK**-kinase inhibiting compound identification for prevention of neuron death)
RE.CNT 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
(1) Dickens, M; Science 1997, V277, P693 HCAPLUS
(2) University of Massachusetts; WO 9918193 A 1999 HCAPLUS
IT **153190-46-6**, **MLK3** kinase
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(JNK- and **MLK**-kinase inhibiting compound identification for prevention of neuron death)
RN 153190-46-6 HCAPLUS
CN Kinase (phosphorylating), gene PTK1 protein (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

=> d all hitstr 135 tot

L35 ANSWER 1 OF 16 HCAPLUS COPYRIGHT 2005 ACS on STN
AN **2004:308510** HCAPLUS
DN 140:316242
ED Entered STN: 15 Apr 2004
TI Method for regulating expression of genes by modulating the expression of H19 gene and use for finding out angiogenesis-controlling genes

IN Hochberg, Abraham; Ayesh, Suhail; Poradosu, Enrique
PA Yissum Research and Development, Israel; McInnis, Patricia
SO PCT Int. Appl., 24 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM C12N
CC 3-4 (Biochemical Genetics)
Section cross-reference(s): 13
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2004031359	A2	20040415	WO 2003-US31306	20031003
WO 2004031359	A3	20041202		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRAI US 2002-415528P P 20021003
CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 2004031359	ICM	C12N

AB The present invention relates to method for regulating expression of genes by modulating the expression of H19 gene and use for finding out clusters of angiogenesis-controlling genes and clusters of ischemic-stress induced genes. A bladder carcinoma cell line, which endogenously does not express H19 RNA, shows a marked difference in gene-expression patterns when transfected with H19 sense, as compared with the gene-expression patterns of the same cell line, when transfected with the H19 antisense. In particular, the expression pattern with cells transfected with the H19 sense, showed a marked increase in two unique groups of genes: one group that controls angiogenesis, and another group of genes which protects cells against ischemic stress.
ST regulation expression human H19 angiogenesis controlling ischemic stress gene
IT Angiogenesis
(-controlling gene; regulating expression of genes by modulating expression of H19 gene and use for finding out angiogenesis-controlling genes)
IT Gene, animal
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(14-3-3-n protein ETA; regulating expression of genes by modulating expression of H19 gene and use for finding out angiogenesis-controlling genes)
IT Gene, animal
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(CD tyrosine 15-kinase weel hu; regulating expression of genes by modulating expression of H19 gene and use for finding out angiogenesis-controlling genes)
IT Gene, animal
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(CDC2-related protein kinase RISSLRE 3; regulating expression of genes by modulating expression of H19 gene and use for finding out angiogenesis-controlling genes)
IT Gene, animal
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(CDKN2A; regulating expression of genes by modulating expression of H19 gene and use for finding out angiogenesis-controlling genes)
IT Transcription factors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(CP2 (CCAAT box-binding protein 2); regulating expression of genes by modulating expression of H19 gene and use for finding out angiogenesis-controlling genes)
IT Transcription factors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(CREB (cAMP-responsive element-binding); regulating expression of genes by modulating expression of H19 gene and use for finding out angiogenesis-controlling genes)
IT Transcription factors

RL: BSU (Biological study, unclassified); BIOL (Biological study)
(ETR101; regulating expression of genes by modulating expression of H19 gene and use for finding out angiogenesis-controlling genes)

IT Gene, animal
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(H19, modulator; regulating expression of genes by modulating expression of H19 gene and use for finding out angiogenesis-controlling genes)

IT Cyclins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(H; regulating expression of genes by modulating expression of H19 gene and use for finding out angiogenesis-controlling genes)

IT Transcription factors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(HIF-1 (hypoxia-inducible factor 1); regulating expression of genes by modulating expression of H19 gene and use for finding out angiogenesis-controlling genes)

IT Gene, animal
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(HK; regulating expression of genes by modulating expression of H19 gene and use for finding out angiogenesis-controlling genes)

IT Heat-shock proteins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(HSP 70; regulating expression of genes by modulating expression of H19 gene and use for finding out angiogenesis-controlling genes)

IT Cell adhesion molecules
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(ICAM-1 (intercellular adhesion mol. 1), sI-CAM-1; regulating expression of genes by modulating expression of H19 gene and use for finding out angiogenesis-controlling genes)

IT Transcription factors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(ID3 (inhibitor of differentiation 3); regulating expression of genes by modulating expression of H19 gene and use for finding out angiogenesis-controlling genes)

IT Transcription factors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(ISGF-2 (interferon-stimulated gene factor 2); regulating expression of genes by modulating expression of H19 gene and use for finding out angiogenesis-controlling genes)

IT Sarcoma
(Kaposi's; regulating expression of genes by modulating expression of H19 gene and use for finding out angiogenesis-controlling genes)

IT Transcription factors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(NF-.kappa.B (nuclear factor of .kappa. light chain gene enhancer in B-cells), P65 subunit; regulating expression of genes by modulating expression of H19 gene and use for finding out angiogenesis-controlling genes)

IT Gene, animal
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(P16-INK4; regulating expression of genes by modulating expression of H19 gene and use for finding out angiogenesis-controlling genes)

IT Elongation factors (protein formation)
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(RNA POLYMERASE II, SIII; regulating expression of genes by modulating expression of H19 gene and use for finding out angiogenesis-controlling genes)

IT Transcription factors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(RelA; regulating expression of genes by modulating expression of H19 gene and use for finding out angiogenesis-controlling genes)

IT Gene, animal
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(SF; regulating expression of genes by modulating expression of H19 gene and use for finding out angiogenesis-controlling genes)

IT Transcription factors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(SREBP (steroid-responsive element-binding protein); regulating expression of genes by modulating expression of H19 gene and use for finding out angiogenesis-controlling genes)

IT Transcription factors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(STAT6 (signal transducer and activator of transcription 6); regulating expression of genes by modulating expression of H19 gene and use for

finding out angiogenesis-controlling genes)
IT G proteins (guanine nucleotide-binding proteins)
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(TIM-1; regulating expression of genes by modulating expression of H19 gene and use for finding out angiogenesis-controlling genes)
IT Tyrosine kinase receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(Tie; regulating expression of genes by modulating expression of H19 gene and use for finding out angiogenesis-controlling genes)
IT Gene, animal
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(VPF; regulating expression of genes by modulating expression of H19 gene and use for finding out angiogenesis-controlling genes)
IT AIDS (disease)
(aids related hemagioma; regulating expression of genes by modulating expression of H19 gene and use for finding out angiogenesis-controlling genes)
IT Gene, animal
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(c-src; regulating expression of genes by modulating expression of H19 gene and use for finding out angiogenesis-controlling genes)
IT Artery, disease
(coronary; regulating expression of genes by modulating expression of H19 gene and use for finding out angiogenesis-controlling genes)
IT Gene, animal
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(cut [ccaat displacement protein\]; regulating expression of genes by modulating expression of H19 gene and use for finding out angiogenesis-controlling genes)
IT **Nervous system, disease**
(**degeneration**; regulating expression of genes by modulating expression of H19 gene and use for finding out angiogenesis-controlling genes)
IT Glycoproteins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(desmoglein 2; regulating expression of genes by modulating expression of H19 gene and use for finding out angiogenesis-controlling genes)
IT Eye, disease
(diabetic retinopathy; regulating expression of genes by modulating expression of H19 gene and use for finding out angiogenesis-controlling genes)
IT Blood vessel
(endothelium, -specific mol.; regulating expression of genes by modulating expression of H19 gene and use for finding out angiogenesis-controlling genes)
IT Transcription factors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(gene ZFM1; regulating expression of genes by modulating expression of H19 gene and use for finding out angiogenesis-controlling genes)
IT Growth factors, animal
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(hepatoma-derived; regulating expression of genes by modulating expression of H19 gene and use for finding out angiogenesis-controlling genes)
IT Gene, animal
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(human C-1; regulating expression of genes by modulating expression of H19 gene and use for finding out angiogenesis-controlling genes)
IT Cell adhesion molecules
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(intra-, 1; regulating expression of genes by modulating expression of H19 gene and use for finding out angiogenesis-controlling genes)
IT Stress, animal
(ischemic; regulating expression of genes by modulating expression of H19 gene and use for finding out angiogenesis-controlling genes)
IT Eye, disease
(macula, senile degeneration; regulating expression of genes by modulating expression of H19 gene and use for finding out angiogenesis-controlling genes)
IT Angiogenesis
(neovascularization; regulating expression of genes by modulating expression of H19 gene and use for finding out angiogenesis-controlling genes)
IT Blood vessel, disease
(peripheral, obstruction; regulating expression of genes by modulating expression of H19 gene and use for finding out angiogenesis-controlling

genes)
IT Integrins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(plasmic, .beta.-5; regulating expression of genes by modulating expression of H19 gene and use for finding out angiogenesis-controlling genes)
IT Surgery
(plastic; regulating expression of genes by modulating expression of H19 gene and use for finding out angiogenesis-controlling genes)
IT Gene, animal
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(platelet membrane glycoprotein IIIA; regulating expression of genes by modulating expression of H19 gene and use for finding out angiogenesis-controlling genes)
IT Gene, animal
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(proliferating-cell nucleolar antigen p120; regulating expression of genes by modulating expression of H19 gene and use for finding out angiogenesis-controlling genes)
IT Pleiotrophins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(prolifern; regulating expression of genes by modulating expression of H19 gene and use for finding out angiogenesis-controlling genes)
IT Gene, animal
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(protein kinase Map1; regulating expression of genes by modulating expression of H19 gene and use for finding out angiogenesis-controlling genes)
IT Gene, animal
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(protein kinase jnk2 stress-activated; regulating expression of genes by modulating expression of H19 gene and use for finding out angiogenesis-controlling genes)
IT Gene, animal
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(receptor tyrosine kinase ligand lerk-4; regulating expression of genes by modulating expression of H19 gene and use for finding out angiogenesis-controlling genes)
IT Anti-AIDS agents
Antiobesity agents
Antitumor agents
Circulation
Fracture (materials)
Genetic vectors
Human
Obesity
Psoriasis
RNA splicing
Rheumatoid arthritis
Tendon
Wound
Wound healing
(regulating expression of genes by modulating expression of H19 gene and use for finding out angiogenesis-controlling genes)
IT Ezrin
Hepatocyte growth factor
Interleukin 6
Interleukin 8
Midkines
Platelet-derived growth factors
Ribozymes
Transferrin receptors
Tumor necrosis factors
Urokinase-type plasminogen activator receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(regulating expression of genes by modulating expression of H19 gene and use for finding out angiogenesis-controlling genes)
IT Artery, disease
(restenosis; regulating expression of genes by modulating expression of H19 gene and use for finding out angiogenesis-controlling genes)
IT Double stranded RNA
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(small interfering; regulating expression of genes by modulating expression of H19 gene and use for finding out angiogenesis-controlling genes)
IT Ischemia

(stress; regulating expression of genes by modulating expression of H19 gene and use for finding out angiogenesis-controlling genes)
IT Brain, disease
(stroke; regulating expression of genes by modulating expression of H19 gene and use for finding out angiogenesis-controlling genes)
IT Neoplasm
(treatment of; regulating expression of genes by modulating expression of H19 gene and use for finding out angiogenesis-controlling genes)
IT Gene, animal
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(tyk2 non-receptor protein tyrosine kinase; regulating expression of genes by modulating expression of H19 gene and use for finding out angiogenesis-controlling genes)
IT **Gene**, animal
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**tyrosine-protein kinase** jaki; regulating expression of genes by modulating expression of H19 gene and use for finding out angiogenesis-controlling genes)
IT Transforming growth factors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(.alpha.-; regulating expression of genes by modulating expression of H19 gene and use for finding out angiogenesis-controlling genes)
IT Macrophage inflammatory protein 2
Vitronectin receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(.alpha.; regulating expression of genes by modulating expression of H19 gene and use for finding out angiogenesis-controlling genes)
IT Transducins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(.beta.-1; regulating expression of genes by modulating expression of H19 gene and use for finding out angiogenesis-controlling genes)
IT Calcium channel
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(.beta.-3; regulating expression of genes by modulating expression of H19 gene and use for finding out angiogenesis-controlling genes)
IT Transforming growth factors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(.beta.-; regulating expression of genes by modulating expression of H19 gene and use for finding out angiogenesis-controlling genes)
IT 329900-75-6, COX-2
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(COX-2; regulating expression of genes by modulating expression of H19 gene and use for finding out angiogenesis-controlling genes)
IT 62031-54-3, Fibroblast growth factor
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(FGF.alpha.; regulating expression of genes by modulating expression of H19 gene and use for finding out angiogenesis-controlling genes)
IT 50812-37-8, Glutathione s-transferase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(microsomal; regulating expression of genes by modulating expression of H19 gene and use for finding out angiogenesis-controlling genes)
IT 9001-26-7, COAGULATION FACTOR II 62229-50-9, EGF 67763-96-6, IGF-1 86090-08-6, Angiostatin 106096-92-8, FGF-1 127464-60-2, Vascular endothelial growth factor 143011-72-7, G-CSF 144697-17-6, C-SRC-KINASE 153570-74-2 154531-34-7, HEPARIN BINDING EGF-LIKE GROWTH FACTOR 169494-85-3, Leptin 187888-07-9, Endostatin
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(regulating expression of genes by modulating expression of H19 gene and use for finding out angiogenesis-controlling genes)
IT 679058-77-6 679058-78-7 679058-79-8 679058-80-1
RL: PRP (Properties)
(unclaimed sequence; method for regulating expression of genes by modulating the expression of H19 gene and use for finding out angiogenesis-controlling genes)

L35 ANSWER 2 OF 16 HCAPLUS COPYRIGHT 2005 ACS on STN
AN **2004:226524** HCAPLUS
ED Entered STN: 21 Mar 2004
TI **MLK1** SAR and structural studies of CEP-1347
AU Hudkins, Robert L.; Meyer, Sheryl L.
CS Medicinal Chemistry, Cephalon, Inc, West Chester, PA, 19380, USA
SO Abstracts of Papers, 227th ACS National Meeting, Anaheim, CA, United States, March 28-April 1, 2004 (2004), MEDI-166 Publisher: American Chemical Society, Washington, D. C.
CODEN: 69FGKM
DT Conference; Meeting Abstract

LA English
AB Our research has focused on developing inhibitors of **mixed lineage kinases** (**MLKs**) for the treatment of neurodegenerative diseases. The **MLKs** function at the MAPKKK level of the stress-activated protein kinase-signaling cascade regulating JNK activation and subsequent cJun phosphorylation leading to neuronal cell death. CEP-1347, active in **Parkinson**'s disease preclin. models and currently in Phase III clin. trials, is an inhibitor of the JNK pathway via **MLK** inhibition and displays a broad neuroprotective profile. Discussed will be **MLK1** SAR and structural studies of CEP-1347.

L35 ANSWER 3 OF 16 HCAPLUS COPYRIGHT 2005 ACS on STN
AN **2004:216615** HCAPLUS
DN 140:367903
ED Entered STN: 18 Mar 2004
TI Targeting the JNK MAPK cascade for inhibition: basic science and therapeutic potential
AU Bogoyevitch, Marie A.; Boehm, Ingrid; Oakley, Aaron; Ketterman, Albert J.; Barr, Renae K.
CS School of Biomedical and Chemical Sciences, Cell Signalling Laboratory, Biochemistry and Molecular Biology, University of Western Australia, Crawley, WA 6009, Australia
SO Biochimica et Biophysica Acta (2004), 1697(1-2), 89-101
CODEN: BBACAQ; ISSN: 0006-3002
PB Elsevier Science B.V.
DT Journal; General Review
LA English
CC 1-0 (Pharmacology)
AB A review. The c-Jun N-terminal protein kinases (JNKs) form one subfamily of the mitogen-activated protein kinase (MAPK) group of serine/threonine protein kinases. The JNKs were first identified by their activation in response to a variety of extracellular stresses and their ability to phosphorylate the N-terminal transactivation domain of the transcription factor c-Jun. One approach to study the function of the JNKs has included in vivo gene knockouts of each of the three JNK genes. While loss of either JNK1 or JNK2 alone appears to have no serious consequences, their combined knockout is embryonic lethal. In contrast, the loss of JNK3 is not embryonic lethal, but rather protects the adult brain from glutamate-induced excitotoxicity. This latter example has generated considerable enthusiasm with JNK3, considered an appropriate target for the treatment of diseases in which neuronal death should be prevented (e.g. stroke, Alzheimer's and **Parkinson**'s diseases). More recently, these gene knockout animals have been used to demonstrate that JNK could provide a suitable target for the protection against obesity and diabetes and that JNKs may act as tumor suppressors. Considerable effort is being directed to the development of chemical inhibitors of the activators of JNKs (e.g. CEP-1347, an inhibitor of the **MLK** family of JNK pathway activators) or of the JNKs themselves (e.g. SP600125, a direct inhibitor of JNK activity). These most commonly used inhibitors have demonstrated efficacy for use in vivo, with the successful intervention to decrease brain damage in animal models (CEP-1347) or to ameliorate some of the symptoms of arthritis in other animal models (SP600125). Alternative peptide-based inhibitors of JNKs are now also in development. The possible identification of allosteric modifiers rather than direct ATP competitors could lead to inhibitors of unprecedented specificity and efficacy.
ST review JNK kinase inhibitor CEP1347 SP600125 peptide
IT Signal transduction, biological
(JNK MAPK cascade inhibitors and their therapeutic potential)
IT Peptides, biological studies
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(JNK MAPK cascade inhibitors and their therapeutic potential)
IT 289898-51-7, JNK1 kinase 289899-93-0, JNK2 kinase 291756-39-3, JNK3 kinase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(JNK MAPK cascade inhibitors and their therapeutic potential)
IT 129-56-6, SP600125 156177-65-0, CEP-1347
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(JNK MAPK cascade inhibitors and their therapeutic potential)
RE.CNT 101 THERE ARE 101 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
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L35 ANSWER 4 OF 16 HCAPLUS COPYRIGHT 2005 ACS on STN
AN **2004:192143** HCAPLUS
DN 140:419104
ED Entered STN: 10 Mar 2004
TI Inhibition of **mixed lineage kinase** 3 attenuates MPP+-induced neurotoxicity in SH-SY5Y cells
AU Mathiasen, Joanne R.; McKenna, Beth Ann W.; Saporito, Michael S.; Ghadge, Ghanashyam D.; Roos, Raymond P.; Holskin, Beverly P.; Wu, Zhi-Liang; Trusko, Stephen P.; Connors, Thomas C.; Maroney, Anna C.; Thomas, Beth Ann; Thomas, Jeffrey C.; Bozyczko-Coyne, Donna
CS Neurobiology, Cephalon, Inc., West Chester, PA, 19380, USA
SO Brain Research (2004), 1003(1,2), 86-97
CODEN: BRREAP; ISSN: 0006-8993
PB Elsevier Science B.V.
DT Journal
LA English
CC 4-3 (Toxicology)
Section cross-reference(s): 14
AB The neuropathol. of **Parkinson**'s Disease has been modeled in exptl. animals following MPTP treatment and in dopaminergic cells in culture treated with the MPTP neurotoxic metabolite, MPP+. MPTP through MPP+ activates the stress-activated c-Jun N-terminal kinase (JNK) pathway in mice and SH-SY5Y neuroblastoma cells. Recently, it was demonstrated that CEP-1347/KT7515 attenuated MPTP-induced nigrostriatal dopaminergic neuron degeneration in mice, as well as MPTP-induced JNK phosphorylation. Presumably, CEP-1347 acts through inhibition of at least one upstream kinase within the **mixed lineage kinase** (**MLK**) family since it has been shown to inhibit **MLK** 1, 2 and 3 in vitro. Activation of the **MLK** family leads to JNK activation. In this study, the potential role of **MLK** and the JNK pathway was examined in MPP+-induced cell **death** of differentiated SH-SY5Y cells using CEP-1347 as a pharmacol. probe and dominant neg. adenoviral constructs to **MLKs**. CEP-1347 inhibited MPP+-induced cell **death** and the morphol. features of **apoptosis**. CEP-1347 also prevented MPP+-induced JNK activation in SH-SY5Y cells. Endogenous **MLK** 3 expression was demonstrated in SH-SY5Y cells through protein levels and RT-PCR. Adenoviral infection of SH-SY5Y cells with a dominant neg. **MLK** 3 construct attenuated the MPP+-mediated increase in activated JNK levels and inhibited neuronal **death** following MPP+ addition compared to cultures infected with a control construct. Adenoviral dominant neg. constructs of two other **MLK** family members (**MLK** 2 and DLK) did not protect against MPP+-induced cell **death**. These studies show that inhibition of the **MLK** 3/JNK pathway attenuates MPP+-mediated SH-SY5Y cell **death** in culture and supports the mechanism of action of CEP-1347 as an **MLK** family inhibitor.
ST **MLK** kinase 3 MPP neurotoxicity SHSY5Y cell; nerve cell **death** **MLK** kinase signaling **Parkinsons** disease
IT Animal cell line
(SH-SY5Y; inhibition of **mixed lineage kinase** 3 attenuates MPP+-induced neurotoxicity in SH-SY5Y

cells)
IT **Apoptosis**
Cell death
Human
Parkinson's disease
Signal transduction, biological
(inhibition of **mixed lineage kinase** 3 attenuates MPP+-induced neurotoxicity in SH-SY5Y cells)
IT **Nerve, neoplasm**
(**neuroblastoma**; inhibition of **mixed lineage kinase** 3 attenuates MPP+-induced neurotoxicity in SH-SY5Y cells)
IT Nerve
(toxicity; inhibition of **mixed lineage kinase** 3 attenuates MPP+-induced neurotoxicity in SH-SY5Y cells)
IT 48134-75-4, MPP+
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(inhibition of **mixed lineage kinase** 3 attenuates MPP+-induced neurotoxicity in SH-SY5Y cells)
IT **153190-46-6, Mixed lineage kinase** 3
155215-87-5, c-Jun N-terminal kinase 156177-65-0, CEP-1347
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibition of **mixed lineage kinase** 3 attenuates MPP+-induced neurotoxicity in SH-SY5Y cells)
RE.CNT 63 THERE ARE 63 CITED REFERENCES AVAILABLE FOR THIS RECORD
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IT **153190-46-6, Mixed lineage kinase 3**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibition of **mixed lineage kinase** 3
attenuates MPP+-induced neurotoxicity in SH-SY5Y cells)
RN 153190-46-6 HCAPLUS
CN Kinase (phosphorylating), gene PTK1 protein (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L35 ANSWER 5 OF 16 HCAPLUS COPYRIGHT 2005 ACS on STN
AN **2004:184769** HCAPLUS
DN 140:301234
ED Entered STN: 08 Mar 2004
TI **Mixed-lineage kinases**: A target for the prevention of neurodegeneration
AU Wang, Leo H.; Besirli, Cagri G.; Johnson, Eugene M., Jr.
CS Departments of Neurology and Molecular Biology & Pharmacology, Washington University School of Medicine, Saint Louis, MO, 63110-1031, USA
SO Annual Review of Pharmacology and Toxicology (2004), 44, 451-474
CODEN: ARPTDI; ISSN: 0362-1642
PB Annual Reviews Inc.
DT Journal; General Review
LA English
CC 14-0 (Mammalian Pathological Biochemistry)
AB A review. The activation of the c-Jun N-terminal kinase (JNK) pathway is critical for naturally occurring neuronal cell **death** during development and may be important for the pathol. neuronal cell **death** of neurodegenerative diseases. The small mol. inhibitor of the **mixed-lineage kinase (MLK)** family of kinases, CEP-1347, inhibits the activation of the JNK pathway and, consequently, the cell **death** in many cell culture and animal models of neuronal **death.** CEP-1347 has the ability not only to inhibit cell **death** but also to maintain the trophic status of neurons in culture. The possible importance of the JNK pathway in neurodegenerative diseases such as Alzheimer's and **Parkinson** 's diseases provides a rationale for the use of CEP-1347 for the treatment of these diseases. CEP-1347 has the potential of not only retarding disease progression but also reversing the severity of symptoms by improving the function of surviving neurons.
ST review JNK kinase neurodegeneration
IT Signal transduction, biological
(JNK kinase pathway dysregulation in neurodegeneration)
IT **Nerve, disease**
(**degeneration**; JNK kinase pathway dysregulation in neurodegeneration)
IT 155215-87-5, c-Jun N-terminal kinase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(JNK kinase pathway dysregulation in neurodegeneration)
RE.CNT 96 THERE ARE 96 CITED REFERENCES AVAILABLE FOR THIS RECORD
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L35 ANSWER 6 OF 16 HCAPLUS COPYRIGHT 2005 ACS on STN
AN **2004:73106** HCAPLUS
DN 140:229244
ED Entered STN: 29 Jan 2004
TI CEP11004, a novel inhibitor of the **mixed lineage kinases**, suppresses **apoptotic death** in dopamine neurons of the substantia nigra induced by 6-hydroxydopamine
AU Ganguly, Anindita; Oo, Tinmarla Frances; Rzhetskaya, Margarita; Pratt, Robert; Yarygina, Olga; Momoi, Takashi; Kholodilov, Nikolai; Burke, Robert E.
CS Department of Neurology, The College of Physicians and Surgeons, Columbia University, New York, NY, USA
SO Journal of Neurochemistry (2004), 88(2), 469-480
CODEN: JONRA9; ISSN: 0022-3042
PB Blackwell Publishing Ltd.
DT Journal
LA English
CC 1-11 (Pharmacology)
Section cross-reference(s): 7, 14
AB There is much evidence that the kinase cascade which leads to the phosphorylation of c-jun plays an important signaling role in the mediation of programmed cell **death.** We have previously shown that c-jun is phosphorylated in a model of induced **apoptotic death** in dopamine neurons of the substantia nigra in vivo. To determine the generality and functional significance of this response, we have examined c-jun phosphorylation and the effect on cell **death** of a novel **mixed lineage kinase** inhibitor, CEP11004, in the 6-hydroxydopamine model of induced **apoptotic death** in dopamine neurons. We found that expression of total c-jun and Ser73-phosphorylated c-jun is increased in this model and both colocalize with **apoptotic** morphol. CEP11004 suppresses **apoptotic death** to levels of 44 and 58% of control values at doses of 1.0 and 3.0 mg/kg, resp. It also suppresses, to approx. equal levels, the number of profiles pos. for the activated form of caspase 9. CEP11004 markedly suppresses striatal dopaminergic fiber loss in these models, to only 22% of control levels. We conclude that c-jun phosphorylation is a general feature of **apoptosis** in living dopamine neurons and that the **mixed lineage kinases** play a functional role as up-stream mediators of cell **death** in these neurons.
ST **apoptosis** cjun phosphorylation kinase signaling CEP11004 neuroprotectant; **Parkinsons** disease **mixed lineage kinase** inhibitor **antiParkinsonian**
IT Transcription factors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(c-jun; **mixed lineage kinase** inhibitor CEP11004 suppresses **apoptotic death** in dopamine neurons of substantia nigra)
IT Brain
(corpus striatum; **mixed lineage kinase** inhibitor CEP11004 suppresses **apoptotic death** in dopamine neurons of substantia nigra)
IT **Nerve, disease**
Nervous system, disease
(degeneration; mixed lineage kinase inhibitor CEP11004 suppresses **apoptotic death** in dopamine **neurons** of substantia nigra)
IT Brain
(dopaminergic system; **mixed lineage kinase** inhibitor CEP11004 suppresses apoptotic death in dopamine neurons of substantia nigra)
IT **Antiparkinsonian agents**
Apoptosis
Human
Parkinson's disease
Phosphorylation, biological
Rattus

Signal transduction, biological
(**mixed lineage kinase** inhibitor CEP11004 suppresses apoptotic death in dopamine **neurons** of substantia nigra)

IT Brain
(substantia nigra, dopaminergic system; **mixed lineage kinase** inhibitor CEP11004 suppresses apoptotic death in dopamine neurons of substantia nigra)

IT Brain
(substantia nigra; **mixed lineage kinase** inhibitor CEP11004 suppresses apoptotic death in dopamine neurons of substantia nigra)

IT **153190-46-6**, **Mixed lineage kinase** 3
155215-87-5, c-Jun **kinase** **179241-70-4**, **Mixed lineage kinase** DLK 180189-96-2, Caspase 9
191808-07-8, **Mixed lineage kinase** 2
250649-03-7, **Mixed lineage kinase** 1
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**mixed lineage kinase** inhibitor CEP11004 suppresses apoptotic death in dopamine neurons of substantia nigra)

IT 504640-06-6, Genbank AY240865 504640-07-7, Genbank AY240866
504640-08-8, Genbank AY240867 504640-09-9, Genbank AY240868
504640-14-6, Genbank AY240864
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(**mixed lineage kinase** inhibitor CEP11004 suppresses apoptotic death in dopamine neurons of substantia nigra)

IT 178404-52-9, CEP 11004
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**mixed lineage kinase** inhibitor CEP11004 suppresses apoptotic death in dopamine neurons of substantia nigra)

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IT **153190-46-6, Mixed lineage kinase 3**
179241-70-4, Mixed lineage kinase
DLK **191808-07-8, Mixed lineage**
kinase 2 250649-03-7, Mixed lineage
kinase 1
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**mixed lineage kinase** inhibitor CEP11004
suppresses apoptotic death in dopamine neurons of substantia nigra)
RN 153190-46-6 HCAPLUS
CN Kinase (phosphorylating), gene PTK1 protein (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 179241-70-4 HCAPLUS
CN Kinase (phosphorylating), protein, DLK (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 191808-07-8 HCAPLUS
CN Kinase (phosphorylating), protein, MLK2 (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 250649-03-7 HCAPLUS
CN Kinase (phosphorylating), protein, MLK1 (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L35 ANSWER 7 OF 16 HCAPLUS COPYRIGHT 2005 ACS on STN
AN **2004:11004** HCAPLUS
DN 141:82110
ED Entered STN: 07 Jan 2004
TI The safety and tolerability of a **mixed lineage**
kinase inhibitor (CEP-1347) in PD
AU Schwid, Steven; Shoulson, Ira; Marek, Ken; Oakes, David; Kieburtz, Karl; Gorbold, Emily; Fahn, Stanley; Goetz, Christopher; Rudolph, Alice; Shinaman, Aileen
CS Parkinson Study Group, Department of Neurology, University of Rochester Medical Center, Rochester, NY, 14642, USA
SO Neurology (2004), 62(2), 330-332
CODEN: NEURAI; ISSN: 0028-3878
PB Lippincott Williams & Wilkins
DT Journal
LA English
CC 1-11 (Pharmacology)
AB CEP-1347 is an inhibitor of members of the **mixed lineage**
kinase family, key signals triggering apoptotic neuronal death. The authors performed a randomized, blinded, placebo-controlled study assessing the safety, tolerability, pharmacokinetics, and acute symptomatic effects of CEP-1347 in 30 patients with **Parkinson**'s disease (PD). In this short-term study, CEP-1347 was safe and well tolerated. It had no acute effect on **parkinsonian** symptoms or levodopa pharmacokinetics, making it well suited for larger and longer studies of its potential to modify the course of PD.
ST CEP 1347 safety tolerability levodopa pharmacokinetics **Parkinson**
's disease
IT **Antiparkinsonian agents**
Drug tolerance
Human
Parkinson's disease
(CEP-1347 safety, tolerability, and effect on levodopa pharmacokinetics in **Parkinson**'s disease)
IT Drug interactions
(pharmacokinetic; CEP-1347 safety, tolerability, and effect on levodopa pharmacokinetics in **Parkinson**'s disease)
IT 156177-65-0, CEP-1347
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological

activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(CEP-1347 safety, tolerability, and effect on levodopa pharmacokinetics in **Parkinson's** disease)
IT 59-92-7, Levodopa, biological studies
RL: PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(CEP-1347 safety, tolerability, and effect on levodopa pharmacokinetics in **Parkinson's** disease)
RE.CNT 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD
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L35 ANSWER 8 OF 16 HCAPLUS COPYRIGHT 2005 ACS on STN
AN **2003:982710** HCAPLUS
DN 140:140035
ED Entered STN: 17 Dec 2003
TI GDNF-deprived sympathetic neurons die via a novel nonmitochondrial pathway
AU Yu, Li-ying; Jokitalo, Eija; Sun, Yun-fu; Mehlen, Patrick; Lindholm, Dan; Saarma, Mart; Arumaee, Urmas
CS Research Program in Molecular Neurobiology, University of Helsinki, Helsinki, FIN-00014, Finland
SO Journal of Cell Biology (2003), 163(5), 987-997
CODEN: JCLBA3; ISSN: 0021-9525
PB Rockefeller University Press
DT Journal
LA English
CC 2-10 (Mammalian Hormones)
AB The mitochondrial death pathway is triggered in cultured sympathetic neurons by deprivation of nerve growth factor (NGF), but the death mechanisms activated by deprivation of other neurotrophic factors are poorly studied. We compared sympathetic neurons deprived of NGF to those deprived of glial cell line-derived neurotrophic factor (GDNF). In contrast to NGF-deprived neurons, GDNF-deprived neurons did not die via the mitochondrial pathway. Indeed, cytochrome c was not released to the cytosol; Bax and caspase-9 and -3 were not involved; overexpressed Bcl-xL did not block the death; and the mitochondrial ultrastructure was not changed. Similarly to NGF-deprived neurons, the death induced by GDNF removal is associated with increased autophagy and requires **multiple lineage kinases**, c-Jun and caspase-2 and -7. Serine 73 of c-Jun was phosphorylated in both NGF- and GDNF-deprived neurons, whereas serine 63 was phosphorylated only in NGF-deprived neurons. In many NGF-deprived neurons, the ultrastructure of the mitochondria was changed. Thus, a novel nonmitochondrial caspase-dependent death pathway is activated in GDNF-deprived sympathetic neurons.
ST GDNF deprivation sympathetic neuron apoptosis cjun caspase mitochondria NGF
IT Proteins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(Bax; GDNF-deprived sympathetic neurons die via activation of caspase 2, -7, c-jun and **MLK**, in comparison to NGF-deprivation-induced neuron apoptosis via mitochondrial pathway)
IT Mitochondria
Newborn
(GDNF-deprived sympathetic neurons die via activation of caspase 2, -7, c-jun and **MLK**, in comparison to NGF-deprivation-induced neuron apoptosis via mitochondrial pathway)
IT Transcription factors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(c-jun; GDNF-deprived sympathetic neurons die via activation of caspase 2, -7, c-jun and **MLK**, in comparison to NGF-deprivation-induced neuron apoptosis via mitochondrial pathway)
IT Neurotrophic factors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(glial-derived; GDNF-deprived sympathetic neurons die via activation of caspase 2, -7, c-jun and **MLK**, in comparison to NGF-deprivation-induced neuron apoptosis via mitochondrial pathway)
IT **Ganglion**
(superior cervical; GDNF-deprived sympathetic neurons die via

activation of caspase 2, -7, c-jun and **MLK**, in comparison to NGF-deprivation-induced neuron **apoptosis** via mitochondrial pathway)

IT **Nerve**
(sympathetic; GDNF-deprived sympathetic neurons die via activation of caspase 2, -7, c-jun and **MLK**, in comparison to NGF-deprivation-induced neuron **apoptosis** via mitochondrial pathway)

IT 9061-61-4, Nerve growth factor 182372-14-1, Caspase-2 189258-14-8, Caspase-7
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(GDNF-deprived sympathetic neurons die via activation of caspase 2, -7, c-jun and **MLK**, in comparison to NGF-deprivation-induced neuron apoptosis via mitochondrial pathway)

IT **651767-79-2, Mixed-lineage protein kinase**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**Mixed-lineage protein kinase**; GDNF-deprived sympathetic neurons die via activation of caspase 2, -7, c-jun and **MLK**, in comparison to NGF-deprivation-induced neuron apoptosis via mitochondrial pathway)

RE.CNT 57 THERE ARE 57 CITED REFERENCES AVAILABLE FOR THIS RECORD

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IT **651767-79-2, Mixed-lineage protein kinase**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**Mixed-lineage protein kinase**; GDNF-deprived sympathetic neurons die via activation of caspase 2, -7, c-jun and **MLK**, in comparison to NGF-deprivation-induced neuron apoptosis via mitochondrial pathway)
RN 651767-79-2 HCAPLUS
CN Kinase (phosphorylating), mixed-lineage protein (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L35 ANSWER 9 OF 16 HCAPLUS COPYRIGHT 2005 ACS on STN
AN **2003:89294** HCAPLUS
DN 139:20080
ED Entered STN: 05 Feb 2003
TI POSH acts as a scaffold for a multiprotein complex that mediates JNK activation in **apoptosis**
AU Xu, Zhiheng; Kukekov, Nickolay V.; Greene, Lloyd A.
CS Department of Pathology, Columbia University, College of Physicians and Surgeons, Center for Neurobiology and Behavior, New York, NY, 10032, USA
SO EMBO Journal (2003), 22(2), 252-261
CODEN: EMJODG; ISSN: 0261-4189
PB Oxford University Press
DT Journal
LA English
CC 13-6 (Mammalian Biochemistry)
AB We report that the multidomain protein POSH (plenty of SH3s) acts as a scaffold for the JNK pathway of neuronal **death**. This pathway consists of a sequential cascade involving activated Rac1/Cdc42, **mixed-lineage kinases** (**MLKs**), MAP kinase kinases (MKKs) 4 and 7, c-Jun N-terminal kinases (JNKs) and c-Jun, and is required for neuronal **death** induced by various means including nerve growth factor (NGF) deprivation. In addition to binding GTP-Rac1 as described previously, we find that POSH binds **MLKs** both in vivo and in vitro, and complexes with MKKs 4 and 7 and with JNKs. POSH overexpression promotes **apoptotic** neuronal **death** and this is suppressed by dominant-neg. forms of **MLKs**, MKK4/7 and c-Jun, and by an **MLK** inhibitor. Moreover, a POSH antisense oligonucleotide and a POSH small interfering RNA (siRNA) suppress c-Jun phosphorylation and neuronal **apoptosis** induced by NGF withdrawal. Thus, POSH appears to function as a scaffold in a multiprotein complex that links activated Rac1 and downstream elements of the JNK **apoptotic** cascade.
ST POSH JNK Jun **MLK** MKK7 kinase cell **death** neuron
IT Proteins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(POSH (plenty of SH3s); POSH acts as scaffold for multiprotein complex that links activated Rac1 and downstream elements of JNK **apoptotic** cascade)
IT G proteins (guanine nucleotide-binding proteins)
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(Rac1; POSH acts as scaffold for multiprotein complex that links activated Rac1 and downstream elements of JNK **apoptotic** cascade)
IT Transcription factors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(c-jun; POSH acts upstream of **MLK** family, MKK4/7 and c-Jun in neuronal **death** pathway)
IT **Nerve, disease**
(**death**; POSH acts as scaffold for multiprotein complex that links activated Rac1 and downstream elements of JNK **neuronal apoptotic** cascade)
IT **Cell death**
(**neuron**; POSH acts as scaffold for multiprotein complex that links activated Rac1 and downstream elements of JNK **neuronal** apoptotic cascade)
IT 155215-87-5, JNK kinase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(POSH acts as scaffold for multiprotein complex that links activated Rac1 and downstream elements of JNK apoptotic cascade)
IT 192230-91-4, MKK4 kinase **260447-83-4, Protein**

kinase MLK 335605-46-4, MKK7 kinase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(POSH acts upstream of **MLK** family, MKK4/7 and c-Jun in neuronal death pathway)
RE.CNT 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD
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IT **260447-83-4, Protein kinase MLK**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(POSH acts upstream of **MLK** family, MKK4/7 and c-Jun in neuronal death pathway)
RN 260447-83-4 HCAPLUS
CN Kinase (phosphorylating), protein, CSAPK-2 (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L35 ANSWER 10 OF 16 HCAPLUS COPYRIGHT 2005 ACS on STN
AN **2002:394536** HCAPLUS
DN 137:304091
ED Entered STN: 28 May 2002
TI **Mixed lineage kinase** family, potential targets for preventing neurodegeneration
AU Maroney, Anna C.; Saporito, Michael S.; Hudkins, Robert L.
CS Cephalon Inc., West Chester, PA, 19380, USA
SO Current Medicinal Chemistry: Central Nervous System Agents (2002), 2(2), 143-155
CODEN: CMCCCO; ISSN: 1568-0150
PB Bentham Science Publishers Ltd.
DT Journal; General Review
LA English
CC 1-0 (Pharmacology)
AB A review. The c-Jun amino terminal kinase (JNK) cascade leading to c-Jun phosphorylation has been implicated in the neuronal cellular response to a variety of external stimuli including free radical oxidative stress, trophic withdrawal, amyloid toxicity and activation by death domain receptor ligands. Although the exact causes of neuronal loss in neurodegenerative diseases remain unknown, it has been hypothesized that response to these environmental stresses may be contributing factors. Agents which block the JNK signaling cascade have been proposed as a therapeutic approach for preventing neuronal cell death observed in a variety of neurodegenerative diseases including **Parkinson**'s, Huntington's, and Alzheimer's disease. The JNKs are regulated through a sequential signaling cascade by a series of upstream kinases including the **mixed lineage kinases (MLKs)**.

Herein, we review the **MLK** family as a therapeutic target and provide evidence with CEP-1347, the most advanced **MLK** inhibitor currently in clin. trails for **Parkinson**'s disease, that intervention at the **MLK** point in the JNK cascade may reduce the susceptibility of neurons to degenerate.

ST review kinase inhibitor neuroprotectant oxidative stress neuron neurodegenerative disease

IT **Nervous system, disease**
(**degeneration; mixed lineage kinase** family, potential targets for preventing neurodegeneration)

IT Drug delivery systems
Human
Oxidative stress, biological
Signal transduction, biological
(**mixed lineage kinase** family, potential targets for preventing neurodegeneration)

IT Nerve
(neuron; **mixed lineage kinase** family, potential targets for preventing neurodegeneration)

IT Cytoprotective agents
(neuroprotective; **mixed lineage kinase** family, potential targets for preventing neurodegeneration)

IT 155215-87-5, JNK
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**mixed lineage kinase** family, potential targets for preventing neurodegeneration)

IT 156177-65-0, CEP-1347
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**mixed lineage kinase** family, potential targets for preventing neurodegeneration)

RE.CNT 95 THERE ARE 95 CITED REFERENCES AVAILABLE FOR THIS RECORD

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L35 ANSWER 11 OF 16 HCAPLUS COPYRIGHT 2005 ACS on STN
AN **2002:142907** HCAPLUS
DN 136:194260
ED Entered STN: 22 Feb 2002
TI Methods for modulating **multiple lineage kinase proteins** and screening compounds which modulate multiple linease kinase proteins
IN Maroney, Anna; Walton, Kevin M.; Dionne, Craig A.; Neff, Nicola; Knight, Ernest, Jr.; Glicksman, Marcie A.
PA Cephalon, Inc., USA
SO PCT Int. Appl., 114 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM C12Q001-00
CC 1-11 (Pharmacology)
Section cross-reference(s): 28
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2002014536	A2	20020221	WO 2001-US24822	20010808

WO 2002014536 A3 20030130
WO 2002014536 C2 20031218
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
CA 2419985 AA 20020221 CA 2001-2419985 20010808
AU 2001083179 A5 20020225 AU 2001-83179 20010808
EP 1309721 A2 20030514 EP 2001-961958 20010808
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR
NO 2003000658 A 20030409 NO 2003-658 20030210
BG 107623 A 20031128 BG 2003-107623 20030310
PRAI US 2000-637054 A 20000811
WO 2001-US24822 W 20010808

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 2002014536	ICM	C12Q001-00

OS MARPAT 136:194260

AB Methods for identifying compds. which modulate activity of a multiple linease kinase protein and promotes cell survival or cell **death** comprising the steps of contacting the cell containing the multiple linease protein with the compound, determining whether the compound decreases activity of the multiple linease protein, and determining whether the compound promotes cell survival are provided. Methods for identifying compds. which may be useful in the treatment of neurodegenerative disorders and/or inflammation are also provided. Methods for modulating the activity of a **multiple lineage kinase protein** comprising contacting the protein or a cell containing the protein with an indeno- or indolo-compound of the invention are also provided. Methods of treating neurodegenerative disorders and/or inflammation are also provided.

ST **multiple lineage kinase** modulator neuroprotectant inflammation inhibitor; neurodegenerative disorder treatment multiple linage kinase modulator

IT Proteins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(AEX-3, mammalian homolog, phosphorylation of; methods for modulating **multiple lineage kinase proteins** and screening compds. which modulate multiple linease kinase proteins and treatment of neurodegenerative disorders and inflammation)

IT Transcription factors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(AFT2, phosphorylation of; methods for modulating **multiple lineage kinase proteins** and screening compds. which modulate multiple linease kinase proteins and treatment of neurodegenerative disorders and inflammation)

IT Transcription factors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(ELK-1, phosphorylation of; methods for modulating **multiple lineage kinase proteins** and screening compds. which modulate multiple linease kinase proteins and treatment of neurodegenerative disorders and inflammation)

IT Neurotransmission
(cholinergic; methods for modulating **multiple lineage kinase proteins** and screening compds. which modulate multiple linease kinase proteins and treatment of neurodegenerative disorders and inflammation)

IT Interleukin 1
Tumor **necrosis** factors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(induction; methods for modulating **multiple lineage kinase proteins** and screening compds. which modulate multiple linease kinase proteins and treatment of neurodegenerative disorders and inflammation)

IT Anti-inflammatory agents
Drug screening
Molecular cloning
(methods for modulating **multiple lineage**

kinase proteins and screening compds. which modulate multiple linease kinase proteins and treatment of neurodegenerative disorders and inflammation)

IT mRNA
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**multiple lineage kinase** substrate-encoding; methods for modulating **multiple lineage kinase proteins** and screening compds. which modulate multiple linease kinase proteins and treatment of neurodegenerative disorders and inflammation)

IT Cytoprotective agents
(neuroprotective; methods for modulating **multiple lineage kinase proteins** and screening compds. which modulate multiple linease kinase proteins and treatment of neurodegenerative disorders and inflammation)

IT AIDS (disease)
(peripheral neuropathy in; methods for modulating **multiple lineage kinase proteins** and screening compds. which modulate multiple linease kinase proteins and treatment of neurodegenerative disorders and inflammation)

IT **Nerve, disease**
(peripheral **neuropathy**, AIDS; methods for modulating **multiple lineage kinase proteins** and screening compds. which modulate multiple linease kinase proteins and treatment of neurodegenerative disorders and inflammation)

IT Phosphorylation, biological
(protein; methods for modulating **multiple lineage kinase proteins** and screening compds. which modulate multiple linease kinase proteins and treatment of neurodegenerative disorders and inflammation)

IT **153190-46-6P, Multiple lineage kinase** 3 **179241-70-4P**, Dual leucine zipper- bearing kinase **191808-07-8P, Multiple lineage kinase** 2 **250649-03-7P, Multiple lineage kinase** 1
RL: BPN (Biosynthetic preparation); BSU (Biological study, unclassified); BIOL (Biological study); PREP (Preparation)
(methods for modulating **multiple lineage kinase proteins** and screening compds. which modulate multiple linease kinase proteins and treatment of neurodegenerative disorders and inflammation)

IT 201168-14-1, Leucine zipper bearing kinase **260396-80-3, Multiple lineage kinase** 6
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(methods for modulating **multiple lineage kinase proteins** and screening compds. which modulate multiple linease kinase proteins and treatment of neurodegenerative disorders and inflammation)

IT 99533-80-9 121665-29-0 156177-64-9 156177-65-0 187810-82-8 200633-48-3 200636-14-2 260388-67-8 260388-68-9 260388-70-3
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(methods for modulating **multiple lineage kinase proteins** and screening compds. which modulate multiple linease kinase proteins and treatment of neurodegenerative disorders and inflammation)

IT 563-47-3, Methallyl chloride 30418-59-8 35523-34-3, 1,1-Diethoxy-2-hexanone 93282-67-8, 1,1-Diethoxy-2-pentanone 251942-38-8 401573-62-4
RL: RCT (Reactant); RACT (Reactant or reagent)
(methods for modulating **multiple lineage kinase proteins** and screening compds. which modulate multiple linease kinase proteins and treatment of neurodegenerative disorders and inflammation)

IT 174349-12-3P 174349-13-4P 251942-24-2P 251942-39-9P 251942-40-2DP, resin-bound 251942-41-3DP, resin-bound 401573-60-2DP, resin-bound 401573-61-3P 401573-63-5P 401795-07-1P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(methods for modulating **multiple lineage kinase proteins** and screening compds. which modulate multiple linease kinase proteins and treatment of neurodegenerative disorders and inflammation)

IT 251942-28-6P 260388-72-5P 260388-73-6P 260388-76-9P 260388-81-6P 260388-82-7P 401573-64-6P 401573-65-7P 401573-66-8P 401795-14-0P
RL: SPN (Synthetic preparation); PREP (Preparation)

(methods for modulating **multiple lineage kinase proteins** and screening compds. which modulate multiple linease kinase proteins and treatment of neurodegenerative disorders and inflammation)

IT 137632-07-6, ERK1 kinase 137632-08-7, ERK2 kinase 142805-58-1, MEK-1 kinase 150316-14-6, MEK2 kinase 155215-87-5, Jun kinase 192230-91-4, MKK4 kinase 194739-73-6, MKK6 kinase 260402-73-1, Protein kinase ATF2 260402-76-4, Kinase (phosphorylating), protein, ELK1 289898-51-7, JNK1 kinase 289899-93-0, JNK2 kinase 291756-39-3, JNK3 kinase 327046-95-7, MEK5 kinase 335605-46-4, MKK7 kinase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(phosphorylation of; methods for modulating **multiple lineage kinase proteins** and screening compds. which modulate multiple linease kinase proteins and treatment of neurodegenerative disorders and inflammation)

IT 98849-88-8 197850-76-3 204513-73-5 401783-05-9 401783-06-0 401783-07-1 401783-08-2 401783-09-3 401783-10-6 401783-11-7 401783-12-8 401783-13-9 401783-14-0 401783-15-1 401783-16-2 401783-17-3 401783-18-4
RL: PRP (Properties)
(unclaimed sequence; methods for modulating **multiple lineage kinase proteins** and screening compds. which modulate multiple linease kinase proteins)

IT 165245-96-5, p38 Kinase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(.alpha. and .beta. and .delta. and .gamma., phosphorylation of; methods for modulating **multiple lineage kinase proteins** and screening compds. which modulate multiple linease kinase proteins and treatment of neurodegenerative disorders and inflammation)

IT **153190-46-6P, Multiple lineage kinase 3** **179241-70-4P**, Dual leucine zipper- bearing kinase **191808-07-8P, Multiple lineage kinase 2** **250649-03-7P, Multiple lineage kinase 1**
RL: BPN (Biosynthetic preparation); BSU (Biological study, unclassified); BIOL (Biological study); PREP (Preparation)
(methods for modulating **multiple lineage kinase proteins** and screening compds. which modulate multiple linease kinase proteins and treatment of neurodegenerative disorders and inflammation)

RN 153190-46-6 HCAPLUS
CN Kinase (phosphorylating), gene PTK1 protein (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

RN 179241-70-4 HCAPLUS
CN Kinase (phosphorylating), protein, DLK (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

RN 191808-07-8 HCAPLUS
CN Kinase (phosphorylating), protein, MLK2 (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

RN 250649-03-7 HCAPLUS
CN Kinase (phosphorylating), protein, MLK1 (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

IT **260396-80-3, Multiple lineage kinase 6**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(methods for modulating **multiple lineage kinase proteins** and screening compds. which modulate multiple linease kinase proteins and treatment of neurodegenerative disorders and inflammation)

RN 260396-80-3 HCAPLUS
CN Kinase (phosphorylating), protein, MLK6 (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L35 ANSWER 12 OF 16 HCAPLUS COPYRIGHT 2005 ACS on STN
AN **2002:1465** HCAPLUS
DN 136:363246
ED Entered STN: 31 Dec 2001
TI **Mixed lineage kinase** activity of indolocarbazole analogues
AU Murakata, Chikara; Kaneko, Masami; Gessner, George; Angeles, Thelma S.;

Ator, Mark A.; O'Kane, Teresa M.; McKenna, Beth Ann W.; Thomas, Beth Ann; Mathiasen, Joanne R.; Saporito, Michael S.; Bozyczko-Coyne, Donna; Hudkins, Robert L.
CS Kyowa-Hakko Kogyo Co., Ltd., Tokyo, Japan
SO Bioorganic & Medicinal Chemistry Letters (2002), 12(2), 147-150
CODEN: BMCLE8; ISSN: 0960-894X
PB Elsevier Science Ltd.
DT Journal
LA English
CC 1-3 (Pharmacology)
Section cross-reference(s): 7, 28
AB The **MLK1**-3 activity for a series of analogs of the indolocarbazole K-252a is reported. Addition of 3,9-bis-alkylthiomethyl groups to K-252a results in potent and selective **MLK** inhibitors. The in vitro and in vivo neuronal survival promoting activity of bis-isopropylthiomethyl-K-252a (CEP-11004/KT-8138) is reported. CEP-11004 demonstrated protection of the JNK kinase pathway following treatment of cells with MPP+ and demonstrated in vivo protection of dopaminergic terminals with the striatum projecting from neurons within the substantia nigra om mice following administration of MPTP. Thus, inhibition of **MLKs** may be an effective strategy for blocking neurodegeration association with **Parkinson**'s disease.
ST **mixed lineage kinase** inhibitor
indolocarbazole analog
IT **Antiparkinsonian agents**
Signal transduction, biological
(**mixed lineage kinase** inhibitor activity of indolocarbazole analogs in relation to neuroprotectant activity and treatment of **Parkinson**'s disease)
IT Structure-activity relationship
(**mixed lineage kinase**-inhibiting; **mixed lineage kinase** inhibitor activity of indolocarbazole analogs in relation to neuroprotectant activity and treatment of **Parkinson**'s disease)
IT Cytoprotective agents
(neuroprotective; **mixed lineage kinase** inhibitor activity of indolocarbazole analogs in relation to neuroprotectant activity and treatment of **Parkinson**'s disease)
IT Brain, disease
(nigrostriatal degeneration, inhibition of; **mixed lineage kinase** inhibitor activity of indolocarbazole analogs in relation to neuroprotectant activity and treatment of **Parkinson**'s disease)
IT **153190-46-6, Mixed lineage kinase 3**
191808-07-8, Mixed lineage kinase 2
250649-03-7, Mixed lineage kinase 1
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**mixed lineage kinase** inhibitor activity of indolocarbazole analogs in relation to neuroprotectant activity and treatment of **Parkinson**'s disease)
IT 178404-52-9P
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(**mixed lineage kinase** inhibitor activity of indolocarbazole analogs in relation to neuroprotectant activity and treatment of **Parkinson**'s disease)
IT 178404-44-9P
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(**mixed lineage kinase** inhibitor activity of indolocarbazole analogs in relation to neuroprotectant activity and treatment of **Parkinson**'s disease)
IT 178404-45-0P 178404-53-0P 178404-54-1P 178404-55-2P 178404-56-3P
190319-45-0P 424788-51-2P 424788-52-3P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(**mixed lineage kinase** inhibitor activity of indolocarbazole analogs in relation to neuroprotectant activity and treatment of **Parkinson**'s disease)
IT 156177-65-0, CEP 1347
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(**mixed lineage kinase** inhibitor activity
of indolocarbazole analogs in relation to neuroprotectant activity and
treatment of **Parkinson**'s disease)
IT 121664-78-6 178459-03-5
RL: RCT (Reactant); RACT (Reactant or reagent)
(**mixed lineage kinase** inhibitor activity
of indolocarbazole analogs in relation to neuroprotectant activity and
treatment of **Parkinson**'s disease)
IT 200637-29-2P 260388-68-9P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT
(Reactant or reagent)
(**mixed lineage kinase** inhibitor activity
of indolocarbazole analogs in relation to neuroprotectant activity and
treatment of **Parkinson**'s disease)
IT 155215-87-5, JNK kinase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(p46 and p54, inhibition of phosphorylation of; **mixed**
lineage kinase inhibitor activity of indolocarbazole
analogs in relation to neuroprotectant activity and treatment of
Parkinson's disease)
IT 200637-31-6
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of)
RE.CNT 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
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IT **153190-46-6**, **Mixed lineage kinase** 3
191808-07-8, **Mixed lineage kinase** 2
250649-03-7, **Mixed lineage kinase** 1
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**mixed lineage kinase** inhibitor activity
of indolocarbazole analogs in relation to neuroprotectant activity and
treatment of **Parkinson**'s disease)
RN 153190-46-6 HCAPLUS
CN Kinase (phosphorylating), gene PTK1 protein (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 191808-07-8 HCAPLUS
CN Kinase (phosphorylating), protein, MLK2 (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 250649-03-7 HCAPLUS
CN Kinase (phosphorylating), protein, MLK1 (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L35 ANSWER 13 OF 16 HCAPLUS COPYRIGHT 2005 ACS on STN
AN **2001:833276** HCAPLUS
DN 135:371989
ED Entered STN: 16 Nov 2001
TI Preparation of novel multicyclic compounds and their amino acid

derivatives as inhibitors of enzymes such as poly(ADP-ribose) polymerase

IN Ator, Mark A.; Bihovsky, Ron; Chatterjee, Sankar; Dunn, Derek; Hudkins, Robert L.

PA Cephalon, Inc., USA

SO PCT Int. Appl., 209 pp.
CODEN: PIXXD2

DT Patent

LA English

IC ICM C07D209-00

CC 34-2 (Amino Acids, Peptides, and Proteins)
Section cross-reference(s): 1, 7, 28

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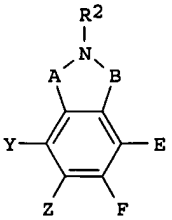
	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001085686	A2	20011115	WO 2001-US14996	20010509
	WO 2001085686	A3	20020530		
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	US 2002028815	A1	20020307	US 2001-850858	20010508
	CA 2409758	AA	20011115	CA 2001-2409758	20010509
	EP 1294725	A2	20030326	EP 2001-935215	20010509
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
	BR 2001010993	A	20030624	BR 2001-10993	20010509
	JP 2004501097	T2	20040115	JP 2001-582287	20010509
	NZ 522539	A	20040528	NZ 2001-522539	20010509
	ZA 2002009065	A	20040209	ZA 2002-9065	20021107
	NO 2002005376	A	20030108	NO 2002-5376	20021108
	BG 107355	A	20030731	BG 2002-107355	20021205
PRAI	US 2000-202947P	P	20000509		
	US 2001-850858	A	20010508		
	WO 2001-US14996	W	20010509		

CLASS

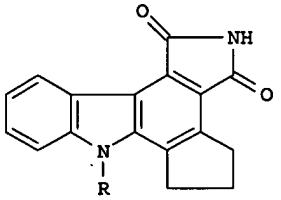
PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 2001085686	ICM	C07D209-00
US 2002028815	ECLA	C07D487/04+209A+209A; C07D487/04+239A+209A; C07D487/04+235A+209A; C07D487/04+237A+209A
JP 2004501097	FTERM	4C050/AA01; 4C050/AA07; 4C050/AA08; 4C050/BB04; 4C050/CC04; 4C050/DD10; 4C050/EE02; 4C050/FF01; 4C050/FF02; 4C050/FF05; 4C050/FF10; 4C050/GG03; 4C050/HH03; 4C050/HH04; 4C086/AA01; 4C086/AA02; 4C086/AA03; 4C086/CB03; 4C086/NA14; 4C086/ZA02; 4C086/ZA15; 4C086/ZA16; 4C086/ZA33; 4C086/ZA36; 4C086/ZA81; 4C086/ZA89; 4C086/ZB11; 4C086/ZB15; 4C086/ZB21; 4C086/ZB26; 4C086/ZC02; 4C086/ZC35

OS MARPAT 135:371989

GI



I



II

AB The title compds. such as penta[a]pyrrolo[3,4-c]carbazole, hexano[a]pyrrolo[3,4-c]carbazole, pyrrolo[3,4-c]carbazole, and furano[a-3,2]pyrrolo[3,4-c]carbazole derivs. [I; A, B = CO, CH(OR3), CH(SR3), CH2, CHR3, CHR3CHR4, CR3R4, COR3, N:CR3, SO, SO2 (wherein R3, R4 = H, optionally substituted lower alkyl or aryl); Y and Z, together with the carbon to which they are attached, form an (un)substituted mono- or

bicyclic aryl or bicyclic heteroaryl, or C3-5 heteroaryl; E, F = lower alkyl or E and F, together with the carbon to which they are attached, form an (un)substituted C4-7 cycloalkyl, C3-6 heterocycloalkyl or heteroaryl, or an (un)substituted heterocycloalkyl endocyclically comprising at least one group G (wherein G = O, S, SO, SO2, NR2, NR2CO, NR2CONR3, NR2SO2, NR3SO2; R2 = H, optionally substituted lower alkyl or alkanoyl, CHO, acetyl, lower alkylsulfonyl, arylsulfonyl, an optionally protected amino acid)] are prepared These compds. are effective in the treatment of diseases or disease states related to the activity of enzymes such as poly(ADP-ribose) polymerase (PARP), vascular endothelial growth factor receptor kinase (VEGFR2 kinase), and **MLK3** kinase (a member of the **mixed lineage kinase** family), including, for example, traumatic central nervous system injuries, neurodegenerative diseases (in particular **Parkinson**'s, Huntington's, or Alzheimer's disease), inflammation, cerebral or cardiac ischemia, endotoxic shock, diabetes, or cellular proliferative disorders (in particular cancer, solid tumors, diabetic retinopathy, intraocular neovascular syndromes, macular degeneration, rheumatoid arthritis, psoriasis, or endometriosis). They also suppress the formation of blood vessels (angiogenesis) and prevent neuronal degradation associated with traumatic central nervous system injuries. Thus, 2H-1,3,4,5,6,7-hexahydrocyclopenta[a]pyrrolo[3,4-c]carbazole-1,3-dione (II; R = H) (preparation given) was treated with NaH in DMF at room temperature for 30 min and condensed with a stirred mixture of Boc-Lys(Boc)-OH dicyclohexylamine salt, TBTU, N-Methylmorpholine, and DMF at room temperature for 1 h, followed by treatment of the product with 4 N HCl in dioxane to give II (R = H-Lys). II (R = H-Lys) showed IC50 of .mu.g/mL against of 22 nM against PARP.

ST clopentapyrrolocarbazole prepn inhibitor poly ADP ribose polymerase; PARP inhibitor multicyclic compd prepn; pyrrolocarbazole prepn inhibitor VEGFR2 kinase; furanopyrrolocarbazole prepn inhibitor VEGFR2 kinase; neurodegenerative disease treatment multicyclic compd prepn; inflammation treatment multicyclic compd prepn; ischemia treatment multicyclic compd prepn; **MLK3** kinase inhibitor multicyclic compd prepn

IT Nervous system
(Huntington's chorea; preparation of novel multicyclic compds. and their amino acid derivs. as inhibitors of enzymes for treatment of diseases related to enzymes such as poly(ADP-ribose) polymerase, VEGFR2 kinase, and **MLK3** kinase)

IT Amides, preparation
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(amino; preparation of novel multicyclic compds. and their amino acid derivs. as inhibitors of enzymes for treatment of diseases related to enzymes such as poly(ADP-ribose) polymerase, VEGFR2 kinase, and **MLK3** kinase)

IT Nervous system
(central, injury; preparation of novel multicyclic compds. and their amino acid derivs. as inhibitors of enzymes for treatment of diseases related to enzymes such as poly(ADP-ribose) polymerase, VEGFR2 kinase, and **MLK3** kinase)

IT **Nervous system**
(**degeneration**; preparation of novel multicyclic compds. and their amino acid derivs. as inhibitors of enzymes for treatment of diseases related to enzymes such as poly(ADP-ribose) polymerase, VEGFR2 kinase, and **MLK3** kinase)

IT Eye, disease
(diabetic retinopathy; preparation of novel multicyclic compds. and their amino acid derivs. as inhibitors of enzymes for treatment of diseases related to enzymes such as poly(ADP-ribose) polymerase, VEGFR2 kinase, and **MLK3** kinase)

IT Cell proliferation
(disorders; preparation of novel multicyclic compds. and their amino acid derivs. as inhibitors of enzymes for treatment of diseases related to enzymes such as poly(ADP-ribose) polymerase, VEGFR2 kinase, and **MLK3** kinase)

IT Uterus, disease
(endometriosis; preparation of novel multicyclic compds. and their amino acid derivs. as inhibitors of enzymes for treatment of diseases related to enzymes such as poly(ADP-ribose) polymerase, VEGFR2 kinase, and **MLK3** kinase)

IT Eye, disease
(intraocular neovascular syndromes; preparation of novel multicyclic compds. and their amino acid derivs. as inhibitors of enzymes for treatment of diseases related to enzymes such as poly(ADP-ribose) polymerase, VEGFR2 kinase, and **MLK3** kinase)

IT Brain, disease
Heart, disease
(ischemia; preparation of novel multicyclic compds. and their amino acid derivs. as inhibitors of enzymes for treatment of diseases related to enzymes such as poly(ADP-ribose) polymerase, VEGFR2 kinase, and **MLK3** kinase)

IT Eye, disease
(macula, degeneration; preparation of novel multicyclic compds. and their amino acid derivs. as inhibitors of enzymes for treatment of diseases related to enzymes such as poly(ADP-ribose) polymerase, VEGFR2 kinase, and **MLK3** kinase)

IT Heterocyclic compounds
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(nitrogen, aromatic; preparation of novel multicyclic compds. and their amino acid derivs. as inhibitors of enzymes for treatment of diseases related to enzymes such as poly(ADP-ribose) polymerase, VEGFR2 kinase, and **MLK3** kinase)

IT Alzheimer's disease
Angiogenesis inhibitors
Anti-inflammatory agents
Antidiabetic agents
Antitumor agents
Parkinson's disease
Psoriasis
Rheumatoid arthritis
(preparation of novel multicyclic compds. and their amino acid derivs. as inhibitors of enzymes for treatment of diseases related to enzymes such as poly(ADP-ribose) polymerase, VEGFR2 kinase, and **MLK3** kinase)

IT Amino acids, preparation
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of novel multicyclic compds. and their amino acid derivs. as inhibitors of enzymes for treatment of diseases related to enzymes such as poly(ADP-ribose) polymerase, VEGFR2 kinase, and **MLK3** kinase)

IT Shock (circulatory collapse)
(septic; preparation of novel multicyclic compds. and their amino acid derivs. as inhibitors of enzymes for treatment of diseases related to enzymes such as poly(ADP-ribose) polymerase, VEGFR2 kinase, and **MLK3** kinase)

IT 374069-00-8P 374069-03-1P 374069-12-2P 374069-14-4P 374069-19-9P
374069-21-3P 374069-22-4P 374069-23-5P 374069-25-7P 374069-26-8P
374069-31-5P 374069-33-7P 374069-35-9P 374069-36-0P 374069-43-9P
374069-44-0P 374069-53-1P 374069-62-2P 374069-75-7P 374070-30-1P
374070-33-4P 374070-38-9P 374070-39-0P 374070-57-2P 374070-59-4P
374070-64-1P 374070-73-2P 374070-77-6P 374070-79-8P 374070-80-1P
374070-83-4P 374070-95-8P 374070-96-9P 374071-01-9P 374071-12-2P
374071-16-6P 374071-28-0P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(preparation of novel multicyclic compds. and their amino acid derivs. as inhibitors of enzymes for treatment of diseases related to enzymes such as poly(ADP-ribose) polymerase, VEGFR2 kinase, and **MLK3** kinase)

IT 154114-97-3P 374068-99-2P 374069-01-9P 374069-02-0P 374069-04-2P
374069-05-3P 374069-06-4P 374069-07-5P 374069-08-6P 374069-09-7P
374069-10-0P 374069-11-1P 374069-13-3P 374069-15-5P 374069-16-6P
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374069-82-6P 374069-83-7P 374069-84-8P 374069-85-9P 374069-87-1P
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374070-47-0P 374070-48-1P 374070-49-2P 374070-50-5P 374070-51-6P
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RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of novel multicyclic compds. and their amino acid derivs. as inhibitors of enzymes for treatment of diseases related to enzymes such as poly(ADP-ribose) polymerase, VEGFR2 kinase, and **MLK3** kinase)

IT 9055-67-8, Poly(ADP-ribose) polymerase 150977-45-0, VEGFR2 kinase **153190-46-6**, **MLK3** kinase
RL: BPR (Biological process); BSU (Biological study, unclassified); MSC (Miscellaneous); BIOL (Biological study); PROC (Process)
(preparation of novel multicyclic compds. and their amino acid derivs. as inhibitors of enzymes for treatment of diseases related to enzymes such as poly(ADP-ribose) polymerase, VEGFR2 kinase, and **MLK3** kinase)

IT 50-00-0, Formaldehyde, reactions 60-34-4 62-55-5, Thioacetamide 62-56-6, Thiourea, reactions 64-19-7, Acetic acid, reactions 68-12-2, DMF, reactions 74-88-4, Methyl iodide, reactions 75-36-5, Acetyl chloride 79-03-8, Propionyl chloride 79-09-4, Propionic acid, reactions 79-30-1, Isobutyryl chloride 79-37-8, Oxalyl chloride 95-15-8, Benzothiophene 98-09-9, Phenylsulfonyl chloride 98-59-9, p-Toluenesulfonyl chloride 100-39-0, Benzyl bromide 105-36-2, Ethyl bromoacetate 107-13-1, Acrylonitrile, reactions 107-92-6, Butyric acid, reactions 108-00-9, N,N-Dimethylethylenediamine 108-12-3, Isovaleryl chloride 108-30-5, Succinic anhydride, reactions 108-55-4, Glutaric anhydride 109-01-3, N-Methylpiperazine 109-86-4, 2-Methoxyethanol 109-89-7, Diethylamine, reactions 109-90-0, Ethyl isocyanate 109-97-7, Pyrrole 110-89-4, Piperidine, reactions 110-91-8, Morpholine, reactions 120-72-9, Indole, reactions 120-92-3, Cyclopentanone 123-75-1, Pyrrolidine, reactions 124-63-0, Methanesulfonyl chloride 140-88-5, Ethyl acrylate 141-43-5, Ethanolamine, reactions 141-75-3, Butyryl chloride 271-89-6, Benzofuran 288-88-0, 1H-1,2,4-Triazole 399-52-0, 5-Fluoroindole 541-59-3, Maleimide 544-92-3, Copper(I) cyanide 557-21-1, Zinc cyanide 591-08-2, N-Acetylthiourea 594-27-4, Tetramethyltin 598-21-0, Bromoacetyl bromide 598-52-7, N-Methylthiourea 614-96-0, 5-Methylindole 623-91-6, Diethyl fumarate 630-08-0, Carbon monoxide, reactions 638-29-9, Valeryl chloride 690-76-6, 2-(tert-Butoxycarbonyl)thioacetamide 762-42-5, Dimethyl acetylenedicarboxylate 933-67-5, 7-Methylindole 999-97-3, Hexamethyldisilazane 1121-92-2 1462-37-9, Benzyl 2-bromoethyl ether 1501-27-5, Glutaric acid monomethyl ester 2038-03-1, 4-(2-Aminoethyl)morpholine 2114-02-5 2133-40-6, L-Proline methyl ester hydrochloride 2812-46-6 3303-84-2, N-tert-Butoxycarbonyl-.beta.-alanine 3878-55-5, Succinic acid monomethyl ester 4023-34-1, Cyclopropanecarbonyl chloride 4377-33-7, 2-Picolyl chloride 4524-93-0, Cyclopentanecarbonyl chloride 4530-20-5, N-tert-Butoxycarbonyl-glycine 4744-50-7, Furo[3,4-b]pyrazine-5,7-dione

5070-13-3, Bis(4-nitrophenyl) carbonate 5332-06-9, 4-Bromobutyronitrile 5332-26-3 5437-45-6, Benzyl bromoacetate 5699-40-1, N-Acetylguanidine 6940-76-7, 1-Chloro-3-iodopropane 6971-44-4, 4-(N-Methylaminomethyl)pyridine 7148-07-4, 1-(Cyclopenten-1-yl)pyrrolidine 7531-52-4, L-Prolinamide 13154-24-0, Triisopropylsilyl chloride 15098-69-8 16503-22-3, N-Methylhistamine dihydrochloride 18107-18-1, Trimethylsilyldiazomethane 19099-93-5, Benzyl 4-oxo-1-piperidinecarboxylate 21035-59-6, 2-(N-Methylaminomethyl)pyridine 24424-99-5, Di-tert-butyl dicarbonate 40594-97-6 49548-40-5 53300-47-3, 2-(Methanesulfonyl)thioacetamide 53654-35-6, 2-Vinylindole 54663-78-4, 2-(Tributylstannyl)thiophene 57260-71-6 57260-73-8, N-tert-Butoxycarbonylethylenediamine 57294-38-9, 4-(tert-Butoxycarbonylamino)butyric acid 76822-35-0 86864-60-0, (2-Bromoethoxy)-tert-butyldimethylsilane 89031-84-5, (3-Bromopropoxy)-tert-butyldimethylsilane 98518-10-6 118486-97-8, 2-(Tributylstannyl)-1-methylpyrrole 124252-41-1, 4-(Tributylstannyl)pyridine 133565-49-8 136088-69-2 138585-09-8, p-(tert-Butyldimethylsilyloxy)benzyl chloride 155440-58-7, 3-(Furan-3-yl)indole 175277-31-3, 2-(tert-Butanesulfonyl)thioacetamide 175334-72-2, 5-Isoxazolecarbothioamide 374071-64-4, 5-(Triisopropylsilyloxy)-2-(1-hydroxycyclopentyl)indole 374071-66-6, 5-Methoxy-2-(1-hydroxycyclopentyl)indole 374071-67-7, 5-(2-Ethoxyethoxy)-2-(1-hydroxycyclopentyl)indole 374071-68-8, 5-[2-(Diethylamino)ethoxy]-2-(1-hydroxycyclopentyl)indole 374071-69-9, 5-[2-(Dimethylamino)ethoxy]-2-(1-hydroxycyclopentyl)indole 374071-70-2, 5-[2-Morpholinoethoxy]-2-(1-hydroxycyclopentyl)indole 374071-71-3, 2-(tert-Butoxycarbonyloxy)thioacetamide 374071-77-9, 2-(2-Buten-2-yl)indole 374071-87-1 374071-90-6, 2-(3-Hepten-3-yl)indole 374071-91-7, 3-(Cyclohexen-1-yl)-1-methylindole 374071-92-8, 2-(2,3-Dihydrofuran-4-yl)indole 374071-93-9 374071-94-0 374071-96-2, 6-Methoxy-2-(1-hydroxycyclopentyl)indole 374071-97-3, 4-Methoxy-2-(1-hydroxycyclopentyl)indole
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of novel multicyclic compds. and their amino acid derivs. as inhibitors of enzymes for treatment of diseases related to enzymes such as poly(ADP-ribose) polymerase, VEGFR2 kinase, and **MLK3** kinase)

IT 90971-74-7P, 3-(Cyclopenten-1-yl)-1-(triisopropylsilyl)pyrrole 118959-02-7P, 2-(Cyclopenten-1-yl)benzofuran 374071-59-7P, 2-(1-Hydroxycyclopentyl)indole 374071-60-0P, 2-(1-Cyclopentenyl)indole 374071-61-1P 374071-62-2P 374071-63-3P 374071-65-5P 374071-72-4P 374071-73-5P 374071-74-6P 374071-75-7P 374071-76-8P 374071-78-0P 374071-79-1P, 2-(Cyclopenten-1-yl)pyrrole 374071-80-4P, 3-(Cyclopenten-1-yl)pyrrole 374071-81-5P, 2-(Cyclopenten-1-yl)-1-(triisopropylsilyl)pyrrole 374071-82-6P 374071-83-7P 374071-84-8P 374071-85-9P, 1,6,7,8-Tetrahydrocyclopenta[g]indole-4,5-dicarboxylic acid 374071-86-0P 374071-88-2P 374071-89-3P 374071-95-1P 374071-98-4P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of novel multicyclic compds. and their amino acid derivs. as inhibitors of enzymes for treatment of diseases related to enzymes such as poly(ADP-ribose) polymerase, VEGFR2 kinase, and **MLK3** kinase)

IT **153190-46-6**, **MLK3** kinase
RL: BPR (Biological process); BSU (Biological study, unclassified); MSC (Miscellaneous); BIOL (Biological study); PROC (Process)
(preparation of novel multicyclic compds. and their amino acid derivs. as inhibitors of enzymes for treatment of diseases related to enzymes such as poly(ADP-ribose) polymerase, VEGFR2 kinase, and **MLK3** kinase)

RN 153190-46-6 HCAPLUS
CN Kinase (phosphorylating), gene PTK1 protein (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L35 ANSWER 14 OF 16 HCAPLUS COPYRIGHT 2005 ACS on STN
AN **2001:522414** HCAPLUS
DN 135:327235
ED Entered STN: 19 Jul 2001
TI CEP-1347 (KT7515), a semisynthetic inhibitor of the **mixed lineage kinase** family
AU Maroney, Anna C.; Finn, James P.; Connors, Thomas J.; Durkin, John T.; Angeles, Thelma; Gessner, George; Xu, Zhiheng; Meyer, Sheryl L.; Savage, Mary J.; Greene, Lloyd A.; Scott, Richard W.; Vaught, Jeffry L.
CS Cephalon Inc., West Chester, PA, 19380, USA
SO Journal of Biological Chemistry (2001), 276(27), 25302-25308

CODEN: JBCHA3; ISSN: 0021-9258
PB American Society for Biochemistry and Molecular Biology
DT Journal
LA English
CC 1-11 (Pharmacology)
AB CEP-1347 (KT7515) promotes neuronal survival at dosages that inhibit activation of the c-Jun amino-terminal kinases (JNKs) in primary embryonic cultures and differentiated PC12 cells after trophic withdrawal and in mice treated with 1-methyl-4-Ph tetrahydropyridine. In an effort to identify mol. target(s) of CEP-1347 in the JNK cascade, JNK1 and known upstream regulators of JNK1 were co-expressed in Cos-7 cells to determine whether CEP-1347 could modulate JNK1 activation. CEP-1347 blocked JNK1 activation induced by members of the **mixed lineage kinase** (**MLK**) family (**MLK3**, **MLK2**, **MLK1**, dual leucine zipper kinase, and leucine zipper kinase). The response was selective because CEP-1347 did not inhibit JNK1 activation in cells induced by kinases independent of the **MLK** cascade. CEP-1347 inhibition of recombinant **MLK** members in vitro was competitive with ATP, resulting in IC50 values ranging from 23 to 51 nM, comparable to inhibitory potencies observed in intact cells. In addition, overexpression of **MLK3** led to **death** in Chinese hamster ovary cells, and CEP-1347 blocked this **death** at doses comparable to those that inhibited **MLK3** kinase activity. These results identify **MLKs** as targets of CEP-1347 in the JNK signaling cascade and demonstrate that CEP-1347 can block **MLK**-induced cell **death**.
ST neuroprotectant CEP1347 **mixed lineage kinase** inhibitor; signal transduction **MLK** JNK1 neuron injury
IT Signal transduction, biological
(CEP-1347 (KT7515), a semisynthetic inhibitor of **mixed lineage kinase** family)
IT **Nerve, disease**
(**injury**; CEP-1347 (KT7515), a semisynthetic inhibitor of **mixed lineage kinase** family)
IT Cytoprotective agents
(neuroprotectants; CEP-1347 (KT7515), a semisynthetic inhibitor of **mixed lineage kinase** family)
IT 156177-65-0, CEP-1347
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(CEP-1347 (KT7515), a semisynthetic inhibitor of **mixed lineage kinase** family)
IT 9031-44-1D, Kinase, dual leucine zipper, leucine zipper
153190-46-6, **Protein kinase MLK3**
191808-07-8, **Protein kinase MLK2**
250649-03-7, **Protein kinase MLK1**
289898-51-7, JNK1
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(CEP-1347 (KT7515), a semisynthetic inhibitor of **mixed lineage kinase** family)
RE.CNT 75 THERE ARE 75 CITED REFERENCES AVAILABLE FOR THIS RECORD
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IT **153190-46-6**, **Protein kinase MLK3**
191808-07-8, **Protein kinase MLK2**
250649-03-7, **Protein kinase MLK1**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(CEP-1347 (KT7515), a semisynthetic inhibitor of **mixed lineage kinase** family)
RN 153190-46-6 HCAPLUS
CN Kinase (phosphorylating), gene PTK1 protein (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 191808-07-8 HCAPLUS
CN Kinase (phosphorylating), protein, MLK2 (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 250649-03-7 HCAPLUS
CN Kinase (phosphorylating), protein, MLK1 (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L35 ANSWER 15 OF 16 HCAPLUS COPYRIGHT 2005 ACS on STN
AN **2001:490787** HCAPLUS
DN 135:208705

ED Entered STN: 08 Jul 2001
TI Evidence for a role of **mixed lineage kinases** in neuronal apoptosis
AU Mota, Monica; Reeder, Melissa; Chernoff, Jonathan; Bazenet, Chantal E.
CS Eisai London Research Laboratories, University College London, London, WC1E 6BT, UK
SO Journal of Neuroscience (2001), 21(14), 4949-4957
CODEN: JNRSDS; ISSN: 0270-6474
PB Society for Neuroscience
DT Journal
LA English
CC 13-6 (Mammalian Biochemistry)
AB Superior cervical ganglion (SCG) sympathetic neurons die by apoptosis when deprived of nerve growth factor (NGF). It has been shown previously that the induction of apoptosis in these neurons at NGF withdrawal requires both the activity of the small GTP-binding protein Cdc42 and the activation of the c-Jun N-terminal kinase (JNK) pathway. The **mixed lineage kinase** 3 (**MLK3**) belongs to a family of mitogen-activated protein (MAP) kinase kinase kinases. **MLK3** contains a Cdc42/Rac interactive-binding (CRIB) domain and activates both the JNK and the p38 MAP kinase pathways. In this study the role of **MLK3** in the induction of apoptosis in sympathetic neurons has been investigated. Overexpression of an active **MLK3** induces activation of the JNK pathway and apoptosis in SCG neurons. In addition, overexpression of kinase dead mutants of **MLK3** blocks apoptosis as well as c-Jun phosphorylation induced by NGF deprivation. More importantly, **MLK3** activity seems to increase by 5 h after NGF withdrawal in both differentiated PC12 cells and SCG neurons. We also show that **MLK3** lies downstream of Cdc42 in the neuronal death pathway. Regulation of **MLK3** in neurons seems to be dependent on **MLK3** activity and possibly on an addnl. cellular component, but not on its binding to Cdc42. These results suggest that **MLK3**, or a closely related kinase, is a physiol. element of NGF withdrawal-induced activation of the Cdc42-c-Jun pathway and neuronal death. **MLK3** therefore could be an interesting therapeutic target in a number of neurodegenerative diseases involving neuronal apoptosis.
ST **MLK3** Jnk kinase Cdc42 sympathetic neuron apoptosis
IT Signal transduction, biological
(evidence for role of **mixed lineage kinases** in Cdc-42-c-Jun pathway in neuronal apoptosis)
IT **Apoptosis**
(evidence for role of **mixed lineage kinases** in **neuronal** apoptosis)
IT G proteins (guanine nucleotide-binding proteins)
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(gene CDC42; evidence for role of **mixed lineage kinases** in Cdc-42-c-Jun pathway in neuronal apoptosis)
IT **Ganglion**
(superior cervical; evidence for role of **mixed lineage kinases** in neuronal **apoptosis**)
IT **Nerve**
(sympathetic; evidence for role of **mixed lineage kinases** in neuronal **apoptosis**)
IT 155215-87-5, Jnk kinase
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(evidence for role of **mixed lineage kinases** in Cdc-42-c-Jun pathway in neuronal apoptosis)
IT **153190-46-6**, **MLK3** kinase
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(evidence for role of **mixed lineage kinases** in neuronal apoptosis)
RE.CNT 50 THERE ARE 50 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
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IT **153190-46-6**, **MLK3** kinase
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(evidence for role of **mixed lineage kinases** in neuronal apoptosis)
RN 153190-46-6 HCAPLUS
CN Kinase (phosphorylating), gene PTK1 protein (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L35 ANSWER 16 OF 16 HCAPLUS COPYRIGHT 2005 ACS on STN
AN **2000:161543** HCAPLUS
DN 132:217150
ED Entered STN: 10 Mar 2000
TI Methods for identification of compounds modulating **multiple lineage kinase proteins**, compound preparation, and therapeutic use
IN Maroney, Anna; Walton, Kevin M.; Dionne, Craig A.; Neff, Nicola; Knight, Ernest, Jr.; Glicksman, Marcie A.
PA Cephalon, Inc., USA
SO PCT Int. Appl., 158 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM G01N033-50
ICS C12Q001-68; G01N033-68; A61K031-40; A61K031-535; A61K031-55
CC 1-12 (Pharmacology)
Section cross-reference(s): 28
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2000013015	A1	20000309	WO 1999-US18864	19990818

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU,

CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL,
IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD,
MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK,
SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG,
KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK,
ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG,
CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

CA 2339539	AA	20000309	CA 1999-2339539	19990818
AU 9956793	A1	20000321	AU 1999-56793	19990818
AU 765637	B2	20030925		
EP 1105728	A1	20010613	EP 1999-943759	19990818
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
TR 200100589	T2	20010723	TR 2001-200100589	19990818
BR 9913190	A	20011211	BR 1999-13190	19990818
JP 2002523780	T2	20020730	JP 2000-567949	19990818
NZ 509612	A	20031031	NZ 1999-509612	19990818
NO 2001000389	A	20010402	NO 2001-389	20010123
BG 105360	A	20011031	BG 2001-105360	20010319
PRAI US 1998-97980P	P	19980826		
WO 1999-US18864	W	19990818		

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 2000013015	ICM	G01N033-50
	ICS	C12Q001-68; G01N033-68; A61K031-40; A61K031-535; A61K031-55

OS MARPAT 132:217150

AB Methods for identifying compds. which modulate activity of a **multiple lineage kinase protein** and promotes cell survival or cell **death** comprise contacting the cell containing the **multiple lineage kinase protein** with the compound, determining whether the compound decreases activity of the **multiple lineage kinase protein**, and determining whether the compound promotes cell survival are provided. Methods for identifying compds. which may be useful in the treatment of neurodegenerative disorders and/or inflammation are also provided. Methods for modulating the activity of a **multiple lineage kinase protein** comprising contacting the protein or a cell containing the protein with an indeno- or indolo- compound of the invention are also provided. Methods of treating neurodegenerative disorders and/or inflammation are also provided.

ST indolo compd **multiple lineage kinase** modulator; indeno compd **multiple lineage kinase** modulator; **MLK** kinase modulator prepn neurodegenerative disease; antiinflammatory **MLK** kinase modulator prepn

IT Proteins, specific or class
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(AEX-3, mammalian homolog; **multiple lineage kinase** modulator identification, compound preparation, and therapeutic use)

IT Animal cell line
(PC12; **multiple lineage kinase** modulator identification, compound preparation, and therapeutic use)

IT Tumor **necrosis** factors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(TNF-.alpha.; **multiple lineage kinase** modulator identification, compound preparation, and therapeutic use)

IT Brain
(cerebral cortex, cortical neuron; **multiple lineage kinase** modulator identification, compound preparation, and therapeutic use)

IT Nerve
(cholinergic; **multiple lineage kinase** modulator identification, compound preparation, and therapeutic use)

IT Ganglion
(ciliary; **multiple lineage kinase** modulator identification, compound preparation, and therapeutic use)

IT **Nerve, disease**
(**death; multiple lineage kinase** modulator identification, compound preparation, and therapeutic use)

IT **Nervous system**
(**degeneration; multiple lineage**

kinase modulator identification, compound preparation, and therapeutic use)

IT Mutation
(dominant neg. **MLK3** mutant; **multiple lineage kinase** modulator identification, compound preparation, and therapeutic use)

IT Embryo, animal
(embryonic motoneuron cell; **multiple lineage kinase** modulator identification, compound preparation, and therapeutic use)

IT Nerve
(motor, embryonic motoneuron cell; **multiple lineage kinase** modulator identification, compound preparation, and therapeutic use)

IT Anti-inflammatory agents
Apoptosis
Cell death
Cytoprotective agents
Drug screening
Nervous system agents
Signal transduction, biological
(**multiple lineage kinase** modulator identification, compound preparation, and therapeutic use)

IT Ciliary neurotrophic factor
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(**multiple lineage kinase** modulator identification, compound preparation, and therapeutic use)

IT Interleukin 1
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(**multiple lineage kinase** modulator identification, compound preparation, and therapeutic use)

IT Interleukin 2
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(**multiple lineage kinase** modulator identification, compound preparation, and therapeutic use)

IT mRNA
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(**multiple lineage kinase** modulator identification, compound preparation, and therapeutic use)

IT **Cell death**
Cell death
Nerve
(**neuron**; **multiple lineage kinase** modulator identification, compound preparation, and therapeutic use)

IT Axon
(outgrowth; **multiple lineage kinase** modulator identification, compound preparation, and therapeutic use)

IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(p38; **multiple lineage kinase** modulator identification, compound preparation, and therapeutic use)

IT Myelin basic protein
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(phosphorylation; **multiple lineage kinase** modulator identification, compound preparation, and therapeutic use)

IT Phosphorylation, biological
(protein; **multiple lineage kinase** modulator identification, compound preparation, and therapeutic use)

IT Ganglion
(spinal; **multiple lineage kinase** modulator identification, compound preparation, and therapeutic use)

IT Ganglion
(sympathetic; **multiple lineage kinase** modulator identification, compound preparation, and therapeutic use)

IT 9012-78-6, Choline acetyltransferase
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(**multiple lineage kinase** modulator identification, compound preparation, and therapeutic use)

IT 9061-61-4, Nerve growth factor
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(**multiple lineage kinase** modulator identification, compound preparation, and therapeutic use)

IT 251942-24-2P 260388-79-2P 260388-81-6P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(**multiple lineage kinase** modulator identification, compound preparation, and therapeutic use)

IT 251942-28-6P 260388-72-5P 260388-73-6P 260388-74-7P 260388-75-8P 260388-76-9P 260388-77-0P 260388-78-1P 260388-80-5P 260388-82-7P 260388-83-8P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(**multiple lineage kinase** modulator identification, compound preparation, and therapeutic use)

IT 99533-80-9 121665-29-0 156177-65-0 156177-67-2 156177-84-3 156177-85-4 167370-93-6 187810-82-8 200632-54-8 200633-48-3 200636-14-2 260388-67-8 260388-68-9 260388-69-0 260388-70-3 260388-71-4
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**multiple lineage kinase** modulator identification, compound preparation, and therapeutic use)

IT 137632-07-6, ERK1 **kinase** 137632-08-7, ERK2 **kinase** 142805-58-1, MEK5 **protein kinase** 142805-58-1 150316-14-6, MEK2 **protein kinase** 153190-46-6, **Multiple lineage kinase** 3 155215-87-5, JNK1 **kinase** 155215-87-5 172308-13-3, MKK3 **protein kinase** 179241-70-4, Dual leucine zipper bearing **kinase** 191808-07-8, **Multiple lineage kinase** 2 192230-91-4, MKK4 **protein kinase** 194739-73-6, MKK6 **protein kinase** 201168-14-1, Leucine zipper-bearing **kinase** 250649-03-7, **Multiple lineage kinase** 1 260396-80-3, **Kinase** (phosphorylating), **protein**, **MLK6** 260402-73-1, **Protein kinase** ATF2 260402-76-4, **Kinase** (phosphorylating), **protein**, ELK1
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(**multiple lineage kinase** modulator identification, compound preparation, and therapeutic use)

IT 251942-40-2DP, polystyrene-divinylbenzene copolymer reaction products 251942-41-3DP, polystyrene-divinylbenzene copolymer reaction products 251942-42-4DP, polystyrene-divinylbenzene copolymer reaction products 251942-43-5P 251942-45-7P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and reaction; **multiple lineage kinase** modulator identification, compound preparation, and therapeutic use)

IT 621-63-6 925-90-6, Ethylmagnesium bromide 3658-95-5 9003-70-7D, Polystyrene-divinylbenzene copolymer, reaction products with diphenylmethanol derivative 18162-48-6, tert-Butyldimethylsilyl chloride 30418-59-8, 3-Aminophenylboronic acid 35523-34-3, 1,1-Diethoxy-2-hexanone 93282-67-8, 1,1-Diethoxy-2-pentanone 115134-35-5D, polystyrene-divinylbenzene copolymer reaction products 174349-12-3 174349-13-4 251942-38-8 251942-39-9
RL: RCT (Reactant); RACT (Reactant or reagent)
(reaction; **multiple lineage kinase** modulator identification, compound preparation, and therapeutic use)

IT 260778-29-8, 1: PN: WO0013015 SEQID: 6 unclaimed DNA 260778-30-1, 2: PN: WO0013015 SEQID: 7 unclaimed DNA 260778-31-2, 3: PN: WO0013015 SEQID: 9 unclaimed DNA 260778-32-3, 4: PN: WO0013015 SEQID: 10 unclaimed DNA 260778-33-4, 5: PN: WO0013015 SEQID: 11 unclaimed DNA 260778-34-5, 6: PN: WO0013015 SEQID: 12 unclaimed DNA 260778-35-6, 7: PN: WO0013015 SEQID: 14 unclaimed DNA 260778-36-7, 8: PN: WO0013015 SEQID: 15 unclaimed DNA 260778-37-8, 9: PN: WO0013015 SEQID: 16 unclaimed DNA
RL: PRP (Properties)
(unclaimed nucleotide sequence; methods for identification of compds. modulating **multiple lineage kinase**

proteins, compound preparation, and therapeutic use)
IT 260778-38-9
RL: PRP (Properties)
(unclaimed protein sequence; methods for identification of compds. modulating **multiple lineage kinase proteins**, compound preparation, and therapeutic use)
IT 98849-88-8 197850-76-3 204513-73-5 260541-57-9 260541-58-0 260541-59-1 260541-60-4
RL: PRP (Properties)
(unclaimed sequence; methods for identification of compds. modulating **multiple lineage kinase proteins**, compound preparation, and therapeutic use)
RE.CNT 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
(1) Angeles, T; ANALYTICAL BIOCHEMISTRY 1996, V236, P49 HCAPLUS
(2) Fang, L; WO 9958982 A 1999 HCAPLUS
(3) Fanger, G; CURRENT OPINION IN GENETICS & DEVELOPMENT 1997, V7(1), P67 HCAPLUS
(4) Glicksman, M; JOURNAL OF NEUROBIOLOGY 1998, V34(4), P361
(5) Glicksman, M; JOURNAL OF NEUROCHEMISTRY 1993, V61(1), P210 HCAPLUS
(6) Hudkins, R; US 5475110 A 1995 HCAPLUS
(7) Kaneko, M; JOURNAL OF MEDICINAL CHEMISTRY 1997, V40(12), P1863 HCAPLUS
(8) Knight, E; ANALYTICAL BIOCHEMISTRY 1997, V247, P376 HCAPLUS
(9) Maroney, A; JOURNAL OF NEUROSCIENCE 1998, V18(1), P104 HCAPLUS
(10) Masami, K; US 5756494 A 1998 HCAPLUS
IT **153190-46-6**, **Multiple lineage kinase 3** **179241-70-4**, Dual leucine zipper bearing **kinase** **191808-07-8**, **Multiple lineage kinase 2** **250649-03-7**, **Multiple lineage kinase 1** **260396-80-3**, **Kinase** (phosphorylating), **protein, MLK6**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(**multiple lineage kinase** modulator identification, compound preparation, and therapeutic use)
RN 153190-46-6 HCAPLUS
CN Kinase (phosphorylating), gene PTK1 protein (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 179241-70-4 HCAPLUS
CN Kinase (phosphorylating), protein, DLK (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 191808-07-8 HCAPLUS
CN Kinase (phosphorylating), protein, MLK2 (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 250649-03-7 HCAPLUS
CN Kinase (phosphorylating), protein, MLK1 (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 260396-80-3 HCAPLUS
CN Kinase (phosphorylating), protein, MLK6 (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

=> b home
FILE 'HOME' ENTERED AT 11:18:52 ON 11 JAN 2005

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=> d his

     (FILE 'HOME' ENTERED AT 13:08:03 ON 11 JAN 2005)

     FILE 'REGISTRY' ENTERED AT 13:08:38 ON 11 JAN 2005
               ACT HAR964S0/A
               ---------
L1            79 SEA FILE=REGISTRY ABB=ON  PLU=ON  MLK? OR KINASE (1A) PROTEIN (
                 ---------

     FILE 'HCAPLUS' ENTERED AT 13:09:02 ON 11 JAN 2005
L2           969 MLK? OR KINASE (1A)PROTEIN (1A) (MLK? OR (MULTIPLE OR MIXED) (1
L3           207 L1
L4          1017 L2-3

     FILE 'BIOSIS' ENTERED AT 13:13:39 ON 11 JAN 2005
L5           506 L1-2
                 E LIU F/AU
                 E LIU Y/AU
L6          1846 E3,E11-12
L7             1 L5 AND L6
L8            85 ((CELL? OR NEURON?) (1A) DEATH OR APOPT? OR NECRO?) AND L6
L9             1 ?PARKIN? AND L8
L10           13 ?PARKIN? AND L6
L11           14 L7 OR L9 OR L10

     FILE 'WPIX' ENTERED AT 13:49:46 ON 11 JAN 2005
L12       138073 (B11-C08? OR C11-C08? OR B11-C10? OR C11-C10? OR D05-H09 OR S03
L13        32287 (B12-K04A5 OR C12-K04A5 OR B14-J01 OR C14-J01 OR B14-J01A3 OR C
L14         2329 (B12-G01B OR C12-G01B OR B14-D03 OR C14-D03)/MC
L15           47 (MLK? OR KINASE (1A)PROTEIN (1A) (MLK? OR (MULTIPLE OR MIXED) (
                 E LIU Y/AU
L16         3351 E3,E10
L17            2 L15 AND L16
L18           45 L15 NOT L17
                 E MLK/CN
                 E MLK/DRN
L19           25 L18 AND L12
L20            6 L19 AND L13-14
L21            1 ((MULTIPLE OR MIXED) (1A) LINKAGE (1A) KINASE)/BIX
L22            6 L20-21
                 SEL AN 5-6 L22
L23            2 E1-2 AND L22
L24           14 (L15 OR L21) AND L13
L25            1 L16 AND L24
                 SEL AN 12-14 L24
L26            3 E3-5 AND L24
L27            0 L26 AND L16
L28            4 L23 OR L26
L29            2 L17 OR L25
L30           45 L18 OR L21
L31            0 L30 AND L14
L32           19 L19 NOT L22
                 SEL AN 6
L33            1 E6 AND L32
L34            5 L33 OR L28

     FILE 'MEDLINE' ENTERED AT 14:31:34 ON 11 JAN 2005
L35          344 L1-2
L36            0 (MULTIPLE OR MIXED) (1A) LINKAGE (1A) KINASE
L37        24584 PARKINSON DISEASE/CT
L38            1 L35 AND L37

     FILE 'EMBASE' ENTERED AT 14:48:55 ON 11 JAN 2005
L39       167654 (TREMOR+NT OR DEGENERATIVE DISEASE+NT OR EXTRAPYRAMIDAL SYMPTOM
L40          330 L1-2
L41            0 (MULTIPLE OR MIXED) (1A) LINKAGE (1A) KINASE
L42       151517 (G3.150 OR G3.120.)/CT
L43           16 L40 AND L39
L44           12 L43 AND L42
                 E LIU Y/AU
L45         3527 E3,E10
L46            2 L45 AND L40
L47           11 L44 NOT L46
                 SEL AN 1 3-5 9
L48            5 E1-5 AND L47
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L49          56 L40 AND L42
L50           2 L49 AND L45
L51           1 L43 AND L45
L52           2 L46 OR L50 OR L51
L53          54 L49 NOT L52
L54          15 L43 NOT L52
L55          58 L53-54
L56           7 L55 AND PY<=1998
                SEL AN 5
L57           1 E6 AND L56
L58           6 L57 OR L48

=> b biosis
FILE 'BIOSIS' ENTERED AT 15:03:12 ON 11 JAN 2005
Copyright (c) 2005 The Thomson Corporation.

FILE COVERS 1969 TO DATE.
CAS REGISTRY NUMBERS AND CHEMICAL NAMES (CNs) PRESENT
FROM JANUARY 1969 TO DATE.

RECORDS LAST ADDED: 5 January 2005 (20050105/ED)

FILE RELOADED: 19 October 2003.

=> d ald 111 tot

L11  ANSWER 1 OF 14  BIOSIS  COPYRIGHT (c) 2005 The Thomson Corporation.  on
     STN
AN   2004:79412  BIOSIS
DN   PREV200400080343
TI   Cyclohexylbisphenol inhibits oxidative stress in 1-methyl-4-phenyl-1,2,3,6-
     tetrahydropyridine (MPTP) mouse model of Parkinson's.
AU   Chalimoniuk, M. [Reprint Author]; Liu, Y.; Kopczuk, D. [Reprint
     Author]; Strosznajder, J. [Reprint Author]
CS   Medical Research Centre, Polish Academy of Sciences, Warsaw, Poland
SO   Journal of Neurochemistry, (December 2003) Vol. 87, No. Supplement 1, pp.
     93. print.
     Meeting Info.: Meeting of the International Society for Neurochemistry
     (ISN). Hong Kong, China. August 03-08, 2003. International Society for
     Neurochemistry.
     CODEN: JONRA9. ISSN: 0022-3042.
DT   Conference; (Meeting)
     Conference; Abstract; (Meeting Abstract)
LA   English
ED   Entered STN: 4 Feb 2004
     Last Updated on STN: 4 Feb 2004
CC   General biology - Symposia, transactions and proceedings   00520
     Biochemistry studies - General   10060
     Biochemistry studies - Nucleic acids, purines and pyrimidines   10062
     Biochemistry studies - Proteins, peptides and amino acids   10064
     Pathology - General   12502
     Pathology - Therapy   12512
     Metabolism - General metabolism and metabolic pathways   13002
     Nervous system - Physiology and biochemistry   20504
     Nervous system - Pathology   20506
     Pharmacology - Neuropharmacology   22024
     Toxicology - General and methods   22501
IT   Major Concepts
        Metabolism; Nervous System (Neural Coordination)
IT   Parts, Structures, & Systems of Organisms
        brain cortex: nervous system; hippocampus: nervous system; midbrain:
        nervous system; striatum: nervous system
IT   Diseases
           Parkinson's disease: nervous system disease,
        chemically-induced, pathology
           Parkinson Disease (MeSH)
IT   Chemicals & Biochemicals
        1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine [MPTP]: toxin; cGMP
        [cyclic GMP]; cyclohexylbisphenol: antiparkinsonian-drug,
        efficacy; free radical: formation; glutathione
IT   Miscellaneous Descriptors
        lipid peroxidation; oxidative stress
ORGN Classifier
        Muridae   86375
     Super Taxa
        Rodentia; Mammalia; Vertebrata; Chordata; Animalia
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Organism Name
C57/BL mouse (common): animal model
Taxa Notes
Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals, Rodents, Vertebrates
RN 28289-54-5 (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine)
28289-54-5 (MPTP)
7665-99-8 (cGMP)
7665-99-8 (cyclic GMP)
70-18-8 (glutathione)

L11 ANSWER 2 OF 14 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation. on STN
AN 2003:304518 BIOSIS
DN PREV200300304518
TI SUBTHALAMIC GLUTAMIC ACID DECARBOXYLASE GENE TRANSFER INDUCES HETEROTRANSMISSION AND NEUROPROTECTION in vivo.
AU Luo, J. [Reprint Author]; Kaplitt, M. G.; Fitzsimons, H. L. [Reprint Author]; Zuzga, D. [Reprint Author]; **Liu, Y.** [Reprint Author]; Oshinsky, M. L. [Reprint Author]; During, M. J. [Reprint Author]
CS Neurosurgery, Thomas Jefferson Univ, Philadelphia, PA, USA
SO Society for Neuroscience Abstract Viewer and Itinerary Planner, (2002) Vol. 2002, pp. Abstract No. 461.2. http://sfn.scholarone.com. cd-rom. Meeting Info.: 32nd Annual Meeting of the Society for Neuroscience. Orlando, Florida, USA. November 02-07, 2002. Society for Neuroscience.
DT Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LA English
ED Entered STN: 2 Jul 2003
Last Updated on STN: 2 Jul 2003
AB **Parkinsons** disease (PD) leads to an alteration in basal ganglia network activity, including disinhibition of the subthalamic nucleus (STN). This leads to excessive activity of the major output nuclei, the substantia nigra pars reticulata (SNr) and internal segment of the globus pallidus (GPi), which impact on motor activity and lead to the cardinal symptoms. Here we describe a genetic approach to test the hypothesis that the glutamatergic neurons of the STN can be induced to express glutamic acid decarboxylase (GAD) via rAAV-mediated gene transfer, and thereby change from an excitatory nucleus to a predominantly inhibitory system. Combined microdialysis and electrophysiology were used to assess the phenotypic shift induced by STN gene transfer. Our data show these excitatory glutamatergic neurons, when driven via electrical stimulation, result in mixed inhibitory responses associated with an increase in GABA release in the SN. This phenotypic shift also results in strong neuroprotection of nigral dopamine neurons in vivo associated with rescue of the **parkinsonian** behavioral phenotype. The combination of vesicular GABA transporter (VGAT) gene transfer with GAD did not confer any additional benefit. Further studies are focused on dissecting the mechanisms whereby GAD with or without VGAT co-expression mediates the phenotypic shift of excitatory neurons at physiological and ultrastructural levels. These data support a novel approach to the treatment of PD and the concept of plasticity between excitatory/inhibitory signaling and heterotransmission in the mammalian brain.
CC General biology - Symposia, transactions and proceedings 00520
Genetics - General 03502
Biochemistry studies - Proteins, peptides and amino acids 10064
Enzymes - General and comparative studies: coenzymes 10802
Nervous system - Physiology and biochemistry 20504
IT Major Concepts
Molecular Genetics (Biochemistry and Molecular Biophysics); Nervous System (Neural Coordination)
IT Parts, Structures, & Systems of Organisms
brain: nervous system; glutamatergic neuron: nervous system; substantia nigra pars reticulata: nervous system; subthalamic nucleus: nervous system
IT Chemicals & Biochemicals
GABA [gamma-aminobutyric acid]: release; glutamic acid decarboxylase [GAD]: expression; vesicular GABA transport [VGAT]: expression
IT Methods & Equipment
electrical stimulation: laboratory techniques; gene transfer: genetic techniques, laboratory techniques
IT Miscellaneous Descriptors
parkinsonian; phenotype
RN 56-12-2 (GABA)
56-12-2 (gamma-aminobutyric acid)

9024-58-2 (glutamic acid decarboxylase)
9024-58-2 (GAD)
GEN VGAT gene [vesicular GABA transport gene]

L11 ANSWER 3 OF 14 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation. on STN
AN 2003:295060 BIOSIS
DN PREV200300295060
TI APOMORPHINE - INDUCED ACUTE WITHDRAWAL IN RATS.
AU White, W. [Reprint Author]; Mattingly, B. A. [Reprint Author]; Duke, A. [Reprint Author]; **Liu, Y.** [Reprint Author]; Dunkman, J. A. [Reprint Author]; Charles, D. [Reprint Author]; White, I. M. [Reprint Author]
CS Psychol Dept, Morehead State Univ, Morehead, KY, USA
SO Society for Neuroscience Abstract Viewer and Itinerary Planner, (2002) Vol. 2002, pp. Abstract No. 400.4. http://sfn.scholarone.com. cd-rom. Meeting Info.: 32nd Annual Meeting of the Society for Neuroscience. Orlando, Florida, USA. November 02-07, 2002. Society for Neuroscience.
DT Conference; (Meeting)
Conference; (Meeting Poster)
Conference; Abstract; (Meeting Abstract)
LA English
ED Entered STN: 25 Jun 2003
Last Updated on STN: 25 Jun 2003
AB Moderate doses of amphetamine (AMPH) produce an immediate stimulant state (during the first several hours post-drug and indicated by excessive locomotion) and an acute withdrawal (around hour 20 post-drug and reflected in hypoctivity), followed by a recovery (beginning around hour 24 post-drug and reflected in a normalization of activity). The purpose of the study was to determine whether the selective dopamine agonist apomorphine (APO) could mimic these changes in activity. Male Wistar rats were housed in open fields (45 cm square) on a 12-12 hour light-dark cycle and with free access to food and water. The animals first were given AMPH (2.0 mg/kg, ip), and then they were given APO hydrochloride (2.0 mg/kg, sc). Control treatments were interspersed with drug administrations, and all treatments occurred at lights on. Distance traveled was quantified with arrays of infrared detectors. APO, like AMPH, produced both hyperactivity for several hours post-drug and hypoactivity around hour 20 post-drug, followed by nomalization of activity beginning around hour 24 post-drug. Dopaminergic systems appear to be involved in acute withdrawal and recovery from AMPH administration.
CC General biology - Symposia, transactions and proceedings 00520
Behavioral biology - General and comparative behavior 07002
Behavioral biology - Animal behavior 07003
Biochemistry studies - General 10060
Biochemistry studies - Proteins, peptides and amino acids 10064
Pathology - Therapy 12512
Nervous system - Physiology and biochemistry 20504
Pharmacology - General 22002
Pharmacology - Neuropharmacology 22024
IT Major Concepts
Behavior; Nervous System (Neural Coordination); Pharmacology
IT Parts, Structures, & Systems of Organisms
dopaminergic system: nervous system
IT Chemicals & Biochemicals
amphetamine: adrenergic antagonist-drug, autonomic-drug; apomorphine hydrochloride: **antiparkinsonian**-drug; dopamine
IT Miscellaneous Descriptors
apomorphine-induced acute withdrawal; hyperactivity; hypoactivity
ORGN Classifier
Muridae 86375
Super Taxa
Rodentia; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
Wistar rat (common): male
rat (common)
Taxa Notes
Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals, Rodents, Vertebrates
RN 300-62-9 (amphetamine)
314-19-2 (apomorphine hydrochloride)
51-61-6 (dopamine)

L11 ANSWER 4 OF 14 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation. on STN
AN 2003:294115 BIOSIS

DN PREV200300294115
TI SYNAPTOPHYSIN ENHANCES THE NEUROPROTECTION OF VMAT2 IN THE MPP+ INDUCED TOXICITY IN Mn9D CELLS.
AU Chen, C. X. [Reprint Author]; Huang, Y. [Reprint Author]; Leak, R. K. [Reprint Author]; **Liu, Y.** [Reprint Author]
CS Neurology, Neurobiology, U. of Pittsburgh Sch of Med, Pittsburgh, PA, USA
SO Society for Neuroscience Abstract Viewer and Itinerary Planner, (2002) Vol. 2002, pp. Abstract No. 343.11. http://sfn.scholarone.com. cd-rom. Meeting Info.: 32nd Annual Meeting of the Society for Neuroscience. Orlando, Florida, USA. November 02-07, 2002. Society for Neuroscience.
DT Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LA English
ED Entered STN: 25 Jun 2003
Last Updated on STN: 25 Jun 2003
AB The neuroprotective role of vesicular monoamine transporters (VMATs) in MPTP induced toxicity, a model for **Parkinsons** disease study, has been indicated by its molecular cloning using CHO fibroblasts, overexpression in non-neuronal cells in vitro and the gene inactivation in mouse. However, there has been lack of direct evidence supporting the role of VMAT2 (neuronal isoform) in dopamine (DA) neuronal survival both in vitro and in vivo, and whether vesicular compartments such as synaptic vesicles (SVs) contribute to the detoxification of MPP+ are unknown. Using a DA cell line MN9D cells as an in vitro system, we have shown that the cells are very sensitive to MPP+ toxicity with a EC50 similar to that of the primary DA neuronal culture. Additionally, MN9D cells express lower levels of secretory vesicle markers such as synaptophysin and SV2, and display DA transporter (DAT) like activity that can be inhibited by mazindol. Overexpression of VMAT2 indeed protects the transformants from MPP+ toxicity, which can be abolished by reserpine. Interestingly, overexpression of synaptophysin alone can induce a resistance of transformants to the toxin compared to that of wild type cells. Furthermore, co-overexpression of VMAT2 and synaptophysin displays a synergetic protective effect in MPP+ toxicity which may result from the increased transport activity. This transformant has also shown more than five fold increase of SV2 expression. In conclusion, the neuroprotection of VMAT2 in DA cells in vitro might be regulated by its vesicular localization and vesicular detoxification capacity which might be enhanced by expression of synaptophysin.
CC General biology - Symposia, transactions and proceedings 00520
Cytology - Animal 02506
Biochemistry studies - General 10060
Biochemistry studies - Proteins, peptides and amino acids 10064
Biophysics - Membrane phenomena 10508
Nervous system - Physiology and biochemistry 20504
Nervous system - Pathology 20506
Pharmacology - Neuropharmacology 22024
Toxicology - General and methods 22501
IT Major Concepts
Biochemistry and Molecular Biophysics; Membranes (Cell Biology); Nervous System (Neural Coordination)
IT Parts, Structures, & Systems of Organisms
dopaminergic neuron: nervous system
IT Chemicals & Biochemicals
MPP: toxicodynamics, neurotoxin; VMAT2 [vesicular monoamine transporter-2]: neuroprotectant; dopamine transporter; synaptophysin
ORGN Classifier
Animalia 33000
Super Taxa
Animalia
Organism Name
MN9D (cell line)
Taxa Notes
Animals

L11 ANSWER 5 OF 14 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation. on STN
AN 2001:497495 BIOSIS
DN PREV200100497495
TI Generation of reactive oxygen species by mitochondrial electron transport chain.
AU **Liu, Y.** [Reprint author]; Schubert, D. [Reprint author]
CS Cell Neurobiol Lab, Salk Inst, San Diego, CA, USA
SO Society for Neuroscience Abstracts, (2001) Vol. 27, No. 1, pp. 536. print. Meeting Info.: 31st Annual Meeting of the Society for Neuroscience. San Diego, California, USA. November 10-15, 2001.

ISSN: 0190-5295.
DT Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LA English
ED Entered STN: 24 Oct 2001
Last Updated on STN: 23 Feb 2002
AB The generation of reactive oxygen species (ROS) by the mitochondrial electron transport chain (ETC), which is composed of four multi-protein complexes named complex I to IV, is believed to be important in the aging process and neurodegenerative diseases such as **Parkinson's** disease. It is commonly assumed that the ubiquinone of complex III is the major site of ROS generation in mitochondrial ETC. We show that the only known physiologically and pathologically relevant site of ROS generation in mitochondrial ETC is limited to the FMN group of complex I. These new insights clarify a widely believed, yet elusive target for delaying aging and for treating mitochondrial ROS-related diseases.
CC General biology - Symposia, transactions and proceedings 00520
Cytology - General 02502
Biochemistry studies - General 10060
Nervous system - Physiology and biochemistry 20504
Nervous system - Pathology 20506
Gerontology - 24500
IT Major Concepts
Aging; Cell Biology; Nervous System (Neural Coordination)
IT Parts, Structures, & Systems of Organisms
complex I, FMN group, mitochondrial electron transport chain protein; mitochondria
IT Diseases
neurodegenerative disease: nervous system disease
Neurodegenerative Diseases (MeSH)
IT Chemicals & Biochemicals
complex III: mitochondrial electron transport chain protein complex, ubiquinone; reactive oxygen species [ROS]: generation
IT Miscellaneous Descriptors
mitochondrial electron transport chain; Meeting Abstract

L11 ANSWER 6 OF 14 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation. on STN
AN 2000:209634 BIOSIS
DN PREV200000209634
TI Effects of decreasing GSH levels in a model for **Parkinson's** disease.
AU Jha, N. [Reprint author]; Jurma, O. [Reprint author]; Lalli, G. [Reprint author]; **Liu, Y.** [Reprint author]; Andersen, J. K. [Reprint author]
CS Dept. of Molecular Biology and Neurosciences, Univ. of Southern California, Los Angeles, CA, 90089, USA
SO Society for Neuroscience Abstracts, (1999) Vol. 25, No. 1-2, pp. 1596. print.
Meeting Info.: 29th Annual Meeting of the Society for Neuroscience. Miami Beach, Florida, USA. October 23-28, 1999. Society for Neuroscience.
ISSN: 0190-5295.
DT Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LA English
ED Entered STN: 24 May 2000
Last Updated on STN: 5 Jan 2002
CC Nervous system - General and methods 20501
Cytology - Animal 02506
Metabolism - General metabolism and metabolic pathways 13002
General biology - Symposia, transactions and proceedings 00520
IT Major Concepts
Cell Biology; Metabolism; Nervous System (Neural Coordination)
IT Diseases
Parkinson's disease: nervous system disease, animal model
Parkinson Disease (MeSH)
IT Chemicals & Biochemicals
glutathione: antioxidant molecule
IT Miscellaneous Descriptors
dopaminergic **cell death**; Meeting Abstract
ORGN Classifier
Muridae 86375
Super Taxa
Rodentia; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
PC12 cell line: rat pheochromocytoma cells

Taxa Notes
Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals, Rodents, Vertebrates
RN 70-18-8 (glutathione)

L11 ANSWER 7 OF 14 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation. on STN
AN 1999:81668 BIOSIS
DN PREV199900081668
TI Increased neuronal cell counts in MAO-B-deficient mouse brain.
AU **Liu, Y.** [Reprint author]; Shih, J. C.; Anderson, J. K. [Reprint author]
CS Ethel Percy Andrus Gerontol. Cent., Univ. S.C., Los Angeles, CA 90089-0191, USA
SO Society for Neuroscience Abstracts, (1998) Vol. 24, No. 1-2, pp. 1946. print.
Meeting Info.: 28th Annual Meeting of the Society for Neuroscience, Part 2. Los Angeles, California, USA. November 7-12, 1998. Society for Neuroscience.
ISSN: 0190-5295.
DT Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
Conference; (Meeting Poster)
LA English
ED Entered STN: 1 Mar 1999
Last Updated on STN: 1 Mar 1999
CC Nervous system - General and methods 20501
Cytology - General 02502
Genetics - General 03502
Biochemistry studies - General 10060
Enzymes - General and comparative studies: coenzymes 10802
General biology - Symposia, transactions and proceedings 00520
IT Major Concepts
Enzymology (Biochemistry and Molecular Biophysics); Molecular Genetics (Biochemistry and Molecular Biophysics); Nervous System (Neural Coordination)
IT Parts, Structures, & Systems of Organisms
brain: nervous system, aging, monoamine oxidase-B deficiency; cerebellar cortex: nervous system; neuronal cell: nervous system, increased count
IT Diseases
Parkinson's disease: nervous system disease
Parkinson Disease (MeSH)
IT Chemicals & Biochemicals
beta-phenylethylamine; monoamine oxidase-B: metabolism
IT Miscellaneous Descriptors
Meeting Abstract; Meeting Poster
ORGN Classifier
Muridae 86375
Super Taxa
Rodentia; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
mouse: model
Taxa Notes
Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals, Rodents, Vertebrates
RN 64-04-0 (beta-phenylethylamine)
9001-66-5 (MONOAMINE OXIDASE-B)

L11 ANSWER 8 OF 14 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation. on STN
AN 1999:51960 BIOSIS
DN PREV199900051960
TI Analysis of molecular mechanisms of neuronal death induced by polyglutamine repeat-expanded Huntington.
AU **Liu, Y. F.**; Deth, R. C.
CS Dep. Pharmacol., Northeast. Univ., Boston, MA 02115, USA
SO Society for Neuroscience Abstracts, (1998) Vol. 24, No. 1-2, pp. 515. print.
Meeting Info.: 28th Annual Meeting of the Society for Neuroscience, Part 1. Los Angeles, California, USA. November 7-12, 1998. Society for Neuroscience.
ISSN: 0190-5295.
DT Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
Conference; (Meeting Slide)

LA English
ED Entered STN: 10 Feb 1999
Last Updated on STN: 10 Feb 1999
CC Nervous system - General and methods 20501
General biology - Symposia, transactions and proceedings 00520
IT Major Concepts
Nervous System (Neural Coordination)
IT Diseases
Huntington's disease: nervous system disease
Huntington Disease (MeSH)
IT Chemicals & Biochemicals
polyglutamine; **MLK2**; human huntingtin gene
IT Miscellaneous Descriptors
neuronal death; CAG repeat; Meeting Abstract; Meeting Slide
ORGN Classifier
Muridae 86375
Super Taxa
Rodentia; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
rat
HN33 cell line: rat hippocampal neuronal cells
Taxa Notes
Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals, Rodents, Vertebrates
RN 26700-71-0Q (polyglutamine)
69864-43-3Q (polyglutamine)

L11 ANSWER 9 OF 14 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation. on STN
AN 1997:419338 BIOSIS
DN PREV199799718541
TI Vesicular monoamine transport, dopamine toxicity and **Parkinson**'s disease.
AU Edwards, R.; Fon, E.; Merickel, A.; Finn, P.; Krantz, D.; **Liu, Y.**
CS UCSF Sch. Med., San Francisco, CA 94143-0435, USA
SO FASEB Journal, (1997) Vol. 11, No. 9, pp. A869.
Meeting Info.: 17th International Congress of Biochemistry and Molecular Biology in conjunction with the Annual Meeting of the American Society for Biochemistry and Molecular Biology. San Francisco, California, USA. August 24-29, 1997.
CODEN: FAJOEC. ISSN: 0892-6638.
DT Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LA English
ED Entered STN: 8 Oct 1997
Last Updated on STN: 8 Oct 1997
CC General biology - Symposia, transactions and proceedings 00520
Cytology - Animal 02506
Biochemistry studies - Proteins, peptides and amino acids 10064
Pathology - General 12502
Metabolism - Proteins, peptides and amino acids 13012
Endocrine - Neuroendocrinology 17020
Nervous system - Anatomy 20502
Nervous system - Physiology and biochemistry 20504
Nervous system - Pathology 20506
Toxicology - General and methods 22501
IT Major Concepts
Biochemistry and Molecular Biophysics; Cell Biology; Endocrine System (Chemical Coordination and Homeostasis); Metabolism; Nervous System (Neural Coordination); Pathology; Toxicology
IT Chemicals & Biochemicals
DOPAMINE
IT Miscellaneous Descriptors
DOPAMINE; DOPAMINE CELL DEGENERATION; DOPAMINE TOXICITY; MONOAMINES; NERVOUS SYSTEM; NERVOUS SYSTEM DISEASE; NEUROTRANSMITTERS; **PARKINSON**'S DISEASE; SECRETORY VESICLE; VESICULAR MONOAMINE TRANSPORT
ORGN Classifier
Muridae 86375
Super Taxa
Rodentia; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
mouse
Taxa Notes
Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals, Rodents, Vertebrates

RN 51-61-6 (DOPAMINE)

L11 ANSWER 10 OF 14 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation. on STN
AN 1997:417867 BIOSIS
DN PREV199799717070
TI Molecular analysis of neurotransmitter transport into secretory vesicles.
AU **Liu, Y.** [Reprint author]; Waites, C.; Krantz, D.; Tan, P.; Edwards, R. H.
CS Dep. Neurol., Univ. Calif. at San Francisco, Sch. Med., San Francisco, CA 94143-0435, USA
SO COLD SPRING HARBOR LABORATORY. Cold Spring Harbor Symp. Quant. Biol., (1996) pp. 747-758. Cold Spring Harbor Symposia on Quantitative Biology; Function and dysfunction in the nervous system.
Publisher: Cold Spring Harbor Laboratory Press, 10 Skyline Drive, Plainview, New York 11803, USA. Series: Cold Spring Harbor Symposia on Quantitative Biology.
Meeting Info.: Meeting.
CODEN: CSHSAZ. ISSN: 0091-7451. ISBN: 0-87969-072-0 (paper), 0-87969-071-2 (cloth).
DT Book; (Book Chapter)
Conference; (Meeting Paper)
LA English
ED Entered STN: 8 Oct 1997
Last Updated on STN: 8 Oct 1997
CC General biology - Symposia, transactions and proceedings 00520
Cytology - Animal 02506
Biochemistry studies - Proteins, peptides and amino acids 10064
Biophysics - Molecular properties and macromolecules 10506
Biophysics - Membrane phenomena 10508
Endocrine - Neuroendocrinology 17020
Nervous system - Physiology and biochemistry 20504
Nervous system - Pathology 20506
IT Major Concepts
Biochemistry and Molecular Biophysics; Cell Biology; Endocrine System (Chemical Coordination and Homeostasis); Membranes (Cell Biology); Nervous System (Neural Coordination)
IT Chemicals & Biochemicals
ACETYLCHOLINE; 1-METHYL-4-PHENYL-1,2,3,6-TETRAHYDROPYRIDINE; MPTP
IT Miscellaneous Descriptors
ACETYLCHOLINE; BEHAVIOR; BIOCHEMISTRY AND BIOPHYSICS; MOLECULAR ANALYSIS; MONOAMINES; MPTP; NERVOUS SYSTEM; NERVOUS SYSTEM DISEASE; NEUROTOXINS; NEUROTRANSMITTER TRANSPORT; **PARKINSON**'S DISEASE; SECRETORY VESICLES; SYNAPTIC TRANSMISSION; VESICULAR MONOAMINE TRANSPORTERS; 1-METHYL-4-PHENYL-1,2,3,6-TETRAHYDROPYRIDINE
ORGN Classifier
Cricetidae 86310
Super Taxa
Rodentia; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
CHO: cell line
Taxa Notes
Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals, Rodents, Vertebrates
ORGN Classifier
Muridae 86375
Super Taxa
Rodentia; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
PC12: cell line
Taxa Notes
Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals, Rodents, Vertebrates
RN 51-84-3 (ACETYLCHOLINE)
28289-54-5 (1-METHYL-4-PHENYL-1,2,3,6-TETRAHYDROPYRIDINE)
28289-54-5 (MPTP)

L11 ANSWER 11 OF 14 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation. on STN
AN 1995:147411 BIOSIS
DN PREV199598161711
TI A molecular analysis of neurotransmitter transport into synaptic vesicles.
AU Roghani, A.; Peter, D.; **Liu, Y.**; Merickel, A.; Feldman, J.; Krantz, D.; Edwards, R. H.
SO Journal of Neurochemistry, (1995) Vol. 64, No. SUPPL. 1, pp. S40.
Meeting Info.: Twenty-sixth Meeting of the American Society for

Neurochemistry. Santa Monica, California, USA. March 5-9, 1995.
CODEN: JONRA9. ISSN: 0022-3042.
DT Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LA English
ED Entered STN: 3 Apr 1995
Last Updated on STN: 4 Apr 1995
CC General biology - Symposia, transactions and proceedings 00520
Biochemistry studies - Nucleic acids, purines and pyrimidines 10062
Biochemistry studies - Proteins, peptides and amino acids 10064
Biophysics - Molecular properties and macromolecules 10506
Endocrine - Neuroendocrinology 17020
Nervous system - Pathology 20506
Psychiatry - Psychopathology, psychodynamics and therapy 21002
Toxicology - General and methods 22501
IT Major Concepts
Behavior; Endocrine System (Chemical Coordination and Homeostasis); Nervous System (Neural Coordination); Toxicology
IT Chemicals & Biochemicals
DOPAMINE; ACETYLCHOLINE
IT Miscellaneous Descriptors
ACETYLCHOLINE; COMPLEMENTARY DNA; DOPAMINE; MEETING ABSTRACT; NEUROPSYCHIATRIC DISEASE; NEUROTOXIN; **PARKINSON**'S DISEASE
ORGN Classifier
Muridae 86375
Super Taxa
Rodentia; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
rat
Taxa Notes
Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals, Rodents, Vertebrates
RN 51-61-6 (DOPAMINE)
51-84-3 (ACETYLCHOLINE)

L11 ANSWER 12 OF 14 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation. on STN
AN 1993:65561 BIOSIS
DN PREV199344031211
TI Computer-assisted test interpretation: Effects on diagnostic decision making.
AU Hillson, S. D.; Connelly, D. P.; **Liu, Y.**
CS Ramsey Clin., Univ. Minn., Minneapolis, Minn, USA
SO Clinical Research, (1992) Vol. 40, No. 3, pp. 769A.
Meeting Info.: Annual Meeting of the Society of General Internal Medicine. Chicago, Illinois, USA. November 6-7, 1992.
CODEN: CLREAS. ISSN: 0009-9279.
DT Conference; (Meeting)
LA English
ED Entered STN: 15 Jan 1993
Last Updated on STN: 15 Jan 1993
CC General biology - Symposia, transactions and proceedings 00520
Pathology - Diagnostic 12504
Pathology - Therapy 12512
Cardiovascular system - Heart pathology 14506
Development and Embryology - Descriptive teratology and teratogenesis 25552
Public health - Health services and medical care 37012
IT Major Concepts
Cardiovascular Medicine (Human Medicine, Medical Sciences); Development; Pathology; Public Health (Allied Medical Sciences)
IT Miscellaneous Descriptors
ABSTRACT; DIAGNOSTIC METHOD; ELECTROCARDIOGRAPHY; PERICARDITIS; THERAPY; WOLFF- **PARKINSON**-WHITE SYNDROME
ORGN Classifier
Hominidae 86215
Super Taxa
Primates; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
human
Taxa Notes
Animals, Chordates, Humans, Mammals, Primates, Vertebrates

L11 ANSWER 13 OF 14 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation. on STN
AN 1993:6982 BIOSIS

DN PREV199395006982
TI Gene transfer of a reserpine-sensitive mechanism of resistance to N-methyl-4-phenylpyridinium.
AU **Liu, Y.**; Roghani, A.; Edwards, R. H. [Reprint author]
CS Dep. Neurology, University California Los Angeles School Medicine, 710 Westwood Plaza, Los Angeles, Calif. 90024-1769, USA
SO Proceedings of the National Academy of Sciences of the United States of America, (1992) Vol. 89, No. 19, pp. 9074-9078.
CODEN: PNASA6. ISSN: 0027-8424.
DT Article
LA English
ED Entered STN: 10 Dec 1992
Last Updated on STN: 13 Dec 1992
AB The toxin N-methyl-1,2,3,6-tetrahydropyridine produces a model of neural degeneration very similar to idiopathic **Parkinson** disease. To understand the cellular mechanisms that modulate susceptibility to its active metabolite N-methyl-4-phenylpyridinium (MPP+), we have transfected a cDNA expression library from the relatively MPP+-resistant rat pheochromocytoma PC12 cells into MPP+-sensitive Chinese hamster ovary (CHO)fibroblasts. Selection of the stable transformants in high concentrations of MPP+ has yielded a clone extremely resistant to the toxin. Reserpin reverses the resistance to MPP+, suggesting that a transport activity protects against this form of toxicity, perhaps by sequestering the toxin within an intracellular compartment. In support of this hypothesis, dopamine loaded into the CHO transformant shows a localized distribution that is distinct from the pattern observed in wild-type cells and is also reversed by reserpine.
CC Cytology - Animal 02506
Genetics - Animal 03506
Biochemistry studies - Nucleic acids, purines and pyrimidines 10062
Biochemistry studies - Proteins, peptides and amino acids 10064
Metabolism - General metabolism and metabolic pathways 13002
Metabolism - Proteins, peptides and amino acids 13012
Endocrine - Neuroendocrinology 17020
Nervous system - Pathology 20506
Pharmacology - Neuropharmacology 22024
Toxicology - General and methods 22501
IT Major Concepts
Cell Biology; Genetics; Metabolism; Nervous System (Neural Coordination); Pharmacology; Toxicology
IT Chemicals & Biochemicals
RESERPINE; DOPAMINE
IT Miscellaneous Descriptors
COMPLEMENTARY DNA; DOPAMINE; **PARKINSON**'S DISEASE MODEL; TOXIN SEQUESTRATION
ORGN Classifier
Cricetidae 86310
Super Taxa
Rodentia; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
hamster
CHO: cell line
Taxa Notes
Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals, Rodents, Vertebrates
ORGN Classifier
Muridae 86375
Super Taxa
Rodentia; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
rat
PC12: cell line
Taxa Notes
Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals, Rodents, Vertebrates
RN 50-55-5 (RESERPINE)
51-61-6 (DOPAMINE)

L11 ANSWER 14 OF 14 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation. on STN
AN 1992:504572 BIOSIS
DN PREV199294123097; BA94:123097
TI A CDNA THAT SUPPRESSES MPP POSITIVE TOXICITY ENCODES A VESICULAR AMINE TRANSPORTER.
AU **LIU Y** [Reprint author]; PETER D; ROGHANI A; SCHULDINER S; PRIVE G G; EISENBERG D; BRECHA N; EDWARDS R H

CS DEP NEUROL, MOL BIOL INST, UNIV CALIF, LOS ANGELES, SCH MED, LOS ANGELES, CALIF 90024-1769, USA
SO Cell, (1992) Vol. 70, No. 4, pp. 539-551.
CODEN: CELLB5. ISSN: 0092-8674.
DT Article
FS BA
LA ENGLISH
OS GENBANK-M97380; GENBANK-M97381
ED Entered STN: 9 Nov 1992
Last Updated on STN: 24 Dec 1992
AB Classical neurotransmitters are transported into synaptic vesicles so that their release can be regulated by neural activity. In addition, the vesicular transport of biogenic amines modulates susceptibility to N-methyl-4-phenylpyridinium (MPP+), the active metabolite of the neurotoxin N-methyl-1,2,3,6-tetrahydropyridine that produces a model of **Parkinson**'s disease. Taking advantage of selection in MPP+, we have used gene transfer followed by plasmid rescue to identify a cDNA clone that encodes a vesicular amine transporter. The sequence predicts a novel mammalian protein with 12 transmembrane domains and homology to a class of bacterial drug resistance transporters. We have detected messenger RNA transcripts for this tranporter only in the adrenal gland. Monoamine cell populations in the brain stem express a distinct but highly related protein.
CC Cytology - Animal 02506
Biochemistry studies - Nucleic acids, purines and pyrimidines 10062
Biochemistry studies - Proteins, peptides and amino acids 10064
Endocrine - Neuroendocrinology 17020
Nervous system - Pathology 20506
In vitro cellular and subcellular studies 32600
IT Major Concepts
Endocrine System (Chemical Coordination and Homeostasis); Nervous System (Neural Coordination)
IT Sequence Data
M97380: GENBANK; M97381: GENBANK
IT Miscellaneous Descriptors
CHINESE HAMSTER OVARY CELLS N METHYL-4-PHENYLPYRIDINIUM MOLECULAR SEQUENCE DATA AMINO ACID SEQUENCE NUCLEOTIDE SEQUENCE GENBANK-M97380 GENBANK-M97381 COMPLEMENTARY DNA NEUROTRANSMITTER RELEASE **PARKINSON**'S DISEASE MODEL
ORGN Classifier
Cricetidae 86310
Super Taxa
Rodentia; Mammalia; Vertebrata; Chordata; Animalia
Taxa Notes
Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals, Rodents, Vertebrates
RN 143967-77-5 (GENBANK-M97380)
143967-79-7 (GENBANK-M97381)

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FOR DETAILS. <<<

=> d all l29 tot

L29 ANSWER 1 OF 2 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
AN 2002-187722 [24] WPIX
CR 2000-086442 [07]
DNC C2002-057884
TI Method of screening a compounds ability to prevent neuronal cell death in mammals, affected with neurological conditions such as Huntington's disease, Alzheimer's disease.
DC B03 B04 D16 S03
IN **LIU, Y F**
PA (LIUY-I) LIU Y F
CYC 1
PI US 2002006606 A1 20020117 (200224)* 29 C12Q001-00
ADT US 2002006606 A1 Provisional US 1998-85439P 19980514, Div ex US 1998-156367 19980917, US 2001-886964 20010621
PRAI US 1998-85439P 19980514; US 1998-156367 19980917;
US 2001-886964 20010621
IC ICM C12Q001-00
AB US2002006606 A UPAB: 20020610
NOVELTY - A compound found to have **Mixed-lineage kinase** (**MLK**) and/or c-Jun N-terminal kinase (JNK) inhibitor activity, is treated with mammalian neurons having activated **MLK** and/or JNK activity. A decrease in the number of dead neurons (in the presence of compound), in comparison to number of dead neurons(in the compounds absence), indicates the anti-neuronal apoptosis effect of the compound.
DETAILED DESCRIPTION - A compound is treated with **MLK** and/or JNK protein and a substrate. The level of JNK and/or **MLK** activity is measured, if the activity of the JNK and/or **MLK** is found to decrease in the presence of the compound (when compared to the activity in the absence of the compound), the compound is confirmed to be a JNK and/or **MLK** inhibitor. This compound is treated with mammalian neurons having activated **Mixed-lineage kinase** (**MLK**) and/or c-Jun N-terminal kinase (JNK) activity. The number of dead neurons is determined. A decrease in the number of dead neurons (in the presence of compound), in comparison to the normal number of dead neurons, indicates the ability of the compound to prevent neuronal death.
USE - For treating mammals with neurological diseases such as Huntington's disease or Alzheimer's disease, which involves nerve cell death by glutamate or kainic acid mediated excitotoxicity (claimed).
Dwg.0/14
FS CPI EPI
FA AB; DCN
MC CPI: B04-F0200E; B04-L04; B11-C08; B11-C08E1; B11-C10; B12-K04A; **B12-K04A5**; B14-D03; B14-H04; **B14-J01**; **B14-J01A3**; B14-J01A4; B14-J01B3; B14-J01B4; B14-J05; B14-J07; B14-N16; B14-N17B; B14-S01; D05-A02B; D05-H09; D05-H14B2

L29 ANSWER 2 OF 2 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
AN 2000-086442 [07] WPIX
CR 2002-187722 [21]
DNN N2000-067845 DNC C2000-024051
TI Method of screening a compounds ability to prevent neuronal cell death in mammals, affected with neurological conditions such as Huntington's disease, Alzheimer's disease.
DC B03 B04 D16 S03
IN **LIU, Y F**
PA (LIUY-I) LIU Y F
CYC 22
PI WO 9958982 A1 19991118 (200007)* EN 62 G01N033-68
RW: AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE
W: CA JP US
EP 1078268 A1 20010228 (200113) EN G01N033-68
R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
US 2002006606 A1 20020117 (200224) 29 C12Q001-00

JP 2002514767 W 20020521 (200236) 71 G01N033-50
US 2002058245 A1 20020516 (200237) C12Q001-00
US 2003148395 A1 20030807 (200358) G01N033-53
US 6811992 B1 20041102 (200472) C12Q001-00

ADT WO 9958982 A1 WO 1999-US10416 19990512; EP 1078268 A1 EP 1999-922972 19990512, WO 1999-US10416 19990512; US 2002006606 A1 Provisional US 1998-85439P 19980514, Div ex US 1998-156367 19980917, US 2001-886964 20010621; JP 2002514767 W WO 1999-US10416 19990512, JP 2000-548734 19990512; US 2002058245 A1 Provisional US 1998-85439P 19980514, Cont of US 1998-156367 19980917, US 2002-42614 20020109; US 2003148395 A1 Provisional US 1998-85439P 19980514, Cont of US 1998-156367 19980917, US 2003-360463 20030205; US 6811992 B1 Provisional US 1998-85439P 19980514, US 1998-156367 19980917

FDT EP 1078268 A1 Based on WO 9958982; JP 2002514767 W Based on WO 9958982

PRAI US 1998-156367 19980917; US 1998-85439P 19980514;
US 2001-886964 20010621; US 2002-42614 20020109;
US 2003-360463 20030205

IC ICM C12Q001-00; G01N033-50; G01N033-53; G01N033-68
ICS C12P021-06; C12Q001-48; C12Q001-68; G01N033-15; G01N033-567

AB WO 9958982 A UPAB: 20020618
NOVELTY - A compound found to have **Mixed-lineage kinase** (**MLK**) and/or c-Jun N-terminal kinase (JNK) inhibitor activity, is treated with mammalian neurons having activated **MLK** and/or JNK activity. A decrease in the number of dead neurons (in the presence of compound), in comparison to number of dead neurons(in the compounds absence), indicates the anti-neuronal apoptosis effect of the compound.
DETAILED DESCRIPTION - A compound is treated with **MLK** and/or JNK protein and a substrate. The level of JNK and/or **MLK** activity is measured, if the activity of the JNK and/or **MLK** is found to decrease in the presence of the compound (when compared to the activity in the absence of the compound), the compound is confirmed to be a JNK and/or **MLK** inhibitor. This compound is treated with mammalian neurons having activated **Mixed-lineage kinase** (**MLK**) and/or c-Jun N-terminal kinase (JNK) activity. The number of dead neurons is determined. A decrease in the number of dead neurons (in the presence of compound), in comparison to the normal number of dead neurons, indicates the ability of the compound to prevent neuronal death.
USE - For treating mammals with neurological diseases such as Huntington's disease or Alzheimer's disease, which involves nerve cell death by glutamate or kainic acid mediated excitotoxicity (claimed).
Dwg.0/14

FS CPI EPI
FA AB; DCN
MC CPI: B04-F02; B04-N02; B11-C08E2; B12-K04A; D05-H09
EPI: S03-E14H

=> d all l34 tot

L34 ANSWER 1 OF 5 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
AN **2002-304059** [34] WPIX
DNC C2002-088410
TI Identifying a compound useful in the treatment of AIDS peripheral neuropathy comprises contacting a cell containing a **multiple linkage kinase** protein with a compound and determining if the compound decreases protein activity.
DC B02 B04 D16
IN DIONNE, C A; GLICKSMAN, M A; KNIGHT, E; MARONEY, A; NEFF, N; WALTON, K M
PA (CEPH-N) CEPHALON INC
CYC 96
PI WO 2002014536 A2 20020221 (200234)* EN 114 C12Q001-00
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW
AU 2001083179 A 20020225 (200245) C12Q001-00
EP 1309721 A2 20030514 (200333) EN C12Q001-48
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR
NO 2003000658 A 20030409 (200333) C12Q000-00
SK 2003000269 A3 20030805 (200360) C12Q001-48
CZ 2003000680 A3 20031112 (200379) C12Q001-48

CN 1458979 A 20031126 (200413) C12Q001-48
MX 2003001218 A1 20030501 (200415) C12Q001-00
ZA 2003001109 A 20040929 (200468) 137 C12Q000-00

ADT WO 2002014536 A2 WO 2001-US24822 20010808; AU 2001083179 A AU 2001-83179 20010808; EP 1309721 A2 EP 2001-961958 20010808, WO 2001-US24822 20010808; NO 2003000658 A WO 2001-US24822 20010808, NO 2003-658 20030210; SK 2003000269 A3 WO 2001-US24822 20010808, SK 2003-269 20010808; CZ 2003000680 A3 WO 2001-US24822 20010808, CZ 2003-680 20010808; CN 1458979 A CN 2001-814001 20010808; MX 2003001218 A1 WO 2001-US24822 20010808, MX 2003-1218 20030210; ZA 2003001109 A ZA 2003-1109 20030210

FDT AU 2001083179 A Based on WO 2002014536; EP 1309721 A2 Based on WO 2002014536; SK 2003000269 A3 Based on WO 2002014536; CZ 2003000680 A3 Based on WO 2002014536; MX 2003001218 A1 Based on WO 2002014536

PRAI US 2000-637054 20000811

IC ICM C12Q000-00; C12Q001-00; C12Q001-48
ICS G01N033-68

AB WO 200214536 A UPAB: 20030227
NOVELTY - Identifying a compound (I), which is useful in the treatment of AIDS peripheral neuropathy, involves contacting a cell or cell extract containing a **multiple linkage kinase** (**MLK**) **protein** with (I) and determining whether (I) decreases or inhibits activity of the **MLK** protein.

DETAILED DESCRIPTION - An INDEPENDENT CLAIM is included for treating a human having AIDS peripheral neuropathy by administering (I).

ACTIVITY - Cytostatic; Gynecological; Opthalmological; Antipsoriatic; Antiinflammatory; Analgesic; Antirheumatic; Antiarthritic; Vulnerary; Cardiant; Antiarteriosclerotic; Vasotropic; Antiparkinsonian; Nootropic; Neuroprotective; Antidiabetic; Anticonvulsant.

Cerebral cortices were dissected from embryonic day 18 rat fetuses and enzymatically digested to obtain a single cell suspension. Cells were seeded at a density of 1.56 multiply 105/cm2 onto poly-ornithine/laminin coated 96 well tissue culture plates in serum-free neural basal medium containing B27 supplements. Plates were coated with a solution of poly-ornithine/laminin (8 micro g/ml each) made in PBS for at least 2 hours at 37 deg. C. On in vitro days 5-7, cortical neurons were exposed to Ab25-35 (20 micro M) either in the presence or absence of a compound of formula (Ic'). Ab25-35 (1 mM) were prepared in deionized-distilled sterile H2O. Relative neuronal survival was determined at 48 hours post-peptide addition using lactate dehydrogenase (LDH) release as an indicator of plasma membrane integrity viability. Data was expressed as percent inhibition of LDH released relative to culture treated with AB25-35 alone. The results obtained were as follows: cortical neurons survival (%) control at 250 nm = 46, 56; motoneurons survival (%) control at 250 nm = 300; mononeurons (%) JNK inhibition at 500 nm = 65; Cos-7 cells DLK (%) JNK inhibition at 500 nm = 63, 73; Cos-7 cells **MLK**-3 (%) JNK inhibition at 500 nm = 98, 99; Cos-7 cells **MLK**-2 (%) JNK inhibition at 500 nm = 89, 67; and Cos-7 cells **MLK1** (%) JNK inhibition at 500 nm = 97, 96.

MECHANISM OF ACTION - **Multiple linkage kinase protein** inhibitor; **Multiple lineage kinase protein** modulator.

USE - For identifying a compound useful in the treatment of AIDS peripheral neuropathy and for treatment of AIDS peripheral neuropathy, in a human (claimed), and for the treatment of diseases involving angiogenesis such as cancer of solid tumors, endometriosis, diabetic retinopathy, psoriasis, hemangioblastoma, as well as other ocular diseases and cancers, solid tumors, neoplasia, inflammatory pain, rheumatoid arthritis, pulmonary fibrosis, myelofibrosis, abnormal wound healing, diseases with cardiovascular end points such as atherosclerosis, restenosis, post-angioplasty restenosis and variety of neurological disorders such as Alzheimer's disease, motor neuron disorder (e.g. amyotrophic lateral sclerosis), Parkinson's disease, cerebrovascular disorder (e.g. stroke, ischemia), Huntington's disease, AIDS dementia, epilepsy, multiple sclerosis, peripheral neuropathies (e.g. those affecting DRG neurons in chemotherapy-associated peripheral neuropathy) including diabetic neuropathy and AIDS peripheral neuropathy; disorders induced by excitatory amino acids; and disorders associated with concessive or penetrating injuries of the brain or spinal cord.

ADVANTAGE - The compounds promotes either cell survival or cell death.

Dwg.0/23

FS CPI
FA AB; GI; DCN
MC CPI: B06-H; **B11-C08E1**; B12-K04E; B14-C01; B14-C09B; B14-F01G; B14-F02D; B14-F02F2; B14-F07; B14-H01B; **B14-J01**; **B14-J01A3**; B14-J01A4; B14-K01; B14-L06; B14-N03; B14-N14;

B14-N16; B14-N17B; B14-N17C; B14-S01; D05-A02B; D05-H09; D05-H10

L34 ANSWER 2 OF 5 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
AN 2001-389716 [41] WPIX
DNC C2001-118750
TI New heterocyclic substituted pyrazolone derivatives are kinase inhibitors, useful for treating or preventing angiogenic disorders, e.g. cancer, endometriosis, diabetic retinopathy, psoriasis.
DC B02 B03
IN SINGH, J; TRIPATHY, R
PA (CEPH-N) CEPHALON INC
CYC 95
PI WO 2001032653 A1 20010510 (200141)* EN 138 C07D405-14
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW
AU 2001015811 A 20010514 (200149) C07D405-14
NO 2002002095 A 20020611 (200252) C07D000-00
EP 1226141 A1 20020731 (200257) EN C07D405-14
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR
US 6455525 B1 20020924 (200266) A61K031-53
KR 2002063179 A 20020801 (200308) C07D405-14
SK 2002000617 A3 20030109 (200309) C07D405-14
CN 1387528 A 20021225 (200324) C07D405-14
CZ 2002001569 A3 20030312 (200324) C07D405-14
HU 2002003203 A2 20030228 (200330) C07D405-14
JP 2003513091 W 20030408 (200333) 164 C07D405-14
BR 2000015568 A 20030610 (200341) C07D405-14
US 2003162775 A1 20030828 (200357) C07D417-02
ZA 2002003492 A 20031029 (200381) 147 C07D000-00
US 6831075 B2 20041214 (200501) A61K031-33
ADT WO 2001032653 A1 WO 2000-US30226 20001101; AU 2001015811 A AU 2001-15811 20001101; NO 2002002095 A WO 2000-US30226 20001101, NO 2002-2095 20020502; EP 1226141 A1 EP 2000-978338 20001101, WO 2000-US30226 20001101; US 6455525 B1 Provisional US 1999-163377P 19991104, US 2000-702191 20001031; KR 2002063179 A KR 2002-705807 20020504; SK 2002000617 A3 WO 2000-US30226 20001101, SK 2002-617 20001101; CN 1387528 A CN 2000-814898 20001101; CZ 2002001569 A3 WO 2000-US30226 20001101, CZ 2002-1569 20001101; HU 2002003203 A2 WO 2000-US30226 20001101, HU 2002-3203 20001101; JP 2003513091 W WO 2000-US30226 20001101, JP 2001-534804 20001101; BR 2000015568 A BR 2000-15568 20001101, WO 2000-US30226 20001101; US 2003162775 A1 Provisional US 1999-163377P 19991104, Cont of US 2000-702191 20001031, US 2002-225670 20020822; ZA 2002003492 A ZA 2002-3492 20020502; US 6831075 B2 Provisional US 1999-163377P 19991104, Cont of US 2000-702191 20001031, US 2002-225670 20020822
FDT AU 2001015811 A Based on WO 2001032653; EP 1226141 A1 Based on WO 2001032653; SK 2002000617 A3 Based on WO 2001032653; CZ 2002001569 A3 Based on WO 2001032653; HU 2002003203 A2 Based on WO 2001032653; JP 2003513091 W Based on WO 2001032653; BR 2000015568 A Based on WO 2001032653; US 2003162775 A1 Cont of US 6455525; US 6831075 B2 Cont of US 6455525
PRAI US 2000-702191 20001031; US 1999-163377P 19991104; US 2002-225670 20020822
IC ICM A61K031-33; A61K031-53; C07D000-00; C07D405-14; C07D417-02
ICS A61K031-415; A61K031-4152; A61K031-4155; A61K031-427; A61K031-433; A61K031-4375; A61K031-4439; A61K031-454; A61K031-496; A61K031-497; A61K031-506; A61K031-5377; A61K031-541; A61K031-555; A61P003-10; A61P007-00; A61P009-00; A61P009-08; A61P015-00; A61P017-06; A61P019-08; A61P019-10; A61P021-00; A61P025-00; A61P025-16; A61P025-28; A61P027-02; A61P029-00; A61P031-12; A61P031-18; A61P035-00; A61P037-02; A61P037-06; A61P043-00; C07D213-00; C07D231-00; C07D231-06; C07D239-00; C07D241-00; C07D251-00; C07D401-04; C07D401-14; C07D403-02; C07D403-04; C07D403-14; C07D405-04; C07D409-04; C07D409-14; C07D413-02; C07D413-04; C07D413-14; C07D417-04; C07D417-14; C07D421-14; C07D487-02; C07D491-056; C07D498-02; C07D513-02; C07D519-00
AB WO 200132653 A UPAB: 20010724
NOVELTY - Heterocyclic substituted pyrazolone derivatives (I) are new.
DETAILED DESCRIPTION - Heterocyclic substituted pyrazolone derivatives of formula (I) and their salts are new:
Het = a heterocycle;

R1 = H; 1-10C alkyl, 2-8C alkenyl, 2-8C alkynyl or heterocycle, each optionally substituted with 1-5 R6; NRaRa, C(=O)Rb, C(=O)NHRa or CO2Rc;

R2, R3 = H; 1-2C alkyl substituted with 1-5 R6; 3-10C alkyl optionally substituted with 1-5 R6; 2-8C alkenyl optionally substituted with 1-5 Ri; 2-6C alkynyl; Cl; Br; I; CN; (CH2)rNRaRa; (CH2)rORc; (CH2)rSRc; (CH2)rC(=O)Rb; (CH2)rCO2Rc; (CH2)rOC(=O)Rb; (CH2)rC(=O)NRaRa; (CH2)rNRaC(=O)Rb; (CH2)rNRaC(=O)ORb; (CH2)rOC(=O)NHRa; (CH2)rNRaS(=O)2Rb; (CH2)rS(=O)2NRaRa; (CH2)rS(O)pRb; or (CH2)rcarbocycle or (CH2)rheterocycle, each optionally substituted with 1-5 R4; or

R2+R3 together may form = heterocycle optionally substituted with 1-4 R4, provided that the heterocycle is other than 2-furanyl; or may form a heterocycle optionally substituted with 1-4 R4, provided that the heterocycle is other than 2-thiazolidinyl or 5-methyl-2 oxazolidinyl;

R4 = H, F, Cl, Br, I, CN, CF3, CF2CF3, NO2, OH, NRaRa, ORc, C(=O)Rb, CO2Rc, OC(=O)Rb, NRaC(=O)Rb, C(=O)NRaRa, OC(=O)NRaRa, NRaC(=O)ORb, NRaS(=O)2Rb, S(=O)2NRaRa, NRaC(=S)Rb, C(=S)NRaRa, NRaC(=O)NRaRa, NRaC(=S)NRaRa, CH=NORc, CH=NRa, CH=NNRaRa, (CH2)rS(O)pRb, O(CH2)qNRaRa, O(CH2)qORc, (CH2)rORd, (CH2)rC(=O)Rd', (CH2)rNHRd, (CH2)rS(O)pRd'; or 1-10C alkyl, 2-8C alkenyl, 2-8C alkynyl, carbocycle or heterocycle, each optionally substituted with 1-5 R6;

R5 = absent or H, 18C alkyl, 2-6C alkenyl, 2-6C alkynyl, (CH2)r(3-6C cycloalkyl) or (CH2)rphenyl;

R6 = 2-8C alkenyl, 2-8C alkynyl, F, Cl, Br, I, CN, CF3, CF2CF3, NO2, CN, NRfRf, ORf, C(=O)Rf, CO2Rf, OC(=O)Rg, NRfC(=O)Rf, C(=O)RfRf, OC(=O)NRfRf, NReC(=O)ORg, NReS(=O)2Rg, S(=O)2NRfRf, NRaC(=S)Rg, C(=S)NRfRf, NRfC(=O)NRfRf, NRfC(=S)NRfRf, CH=NORe, CH=NRe, CH=NNReRe, S(O)pRf, O(CH2)pNRfRf, O(CH2)pORf, ORd, NHRd, C(-O)Rd', S(O)pRd', P(=O)(ORc)2; or 1-6C alkyl, carbocycle or heterocycle, each optionally substituted with 1-5 Rh; or a 5-7C monosaccharide where each hydroxyl of the monosaccharide is optionally replaced by H, 1-4C alkyl, 1-4C alkoxy or OC(=O)(1-4C alkyl);

Ra = H; or 1-6C alkyl, 2-6C alkenyl, 2-6C alkynyl, (CH2)r(3-6C cycloalkyl) or (CH2)rphenyl, each optionally substituted with 1-5 Rh; or 2 Ra together may form (CH2)qO(CH2)q, (CH2)qS(CH2)q or (CH2)m, each optionally substituted with 1-5 Rh;

Rb = 1-6C alkyl, 2-6C alkenyl, 2-6C alkynyl, (CH2)rphenyl or (CH2)rheterocycle, each optionally substituted with 1-5 Rh;

Rc = H; or 1-6C alkyl, 2-6C alkenyl, 2-6C alkynyl, 3-6C cycloalkyl or (CH2)rphenyl, each optionally substituted with 15 Rh;

Rd = the residue of an amino acid after the hydroxyl group of the carboxyl group is removed;

Rd' = the residue of an amino acid after the hydrogen of the amine is removed;

Re = H or 1-6C alkyl;

Rg = 1-6C alkyl or (CH2)rphenyl, each optionally substituted with 1-5 Rh;

Rf = Rg or H;

Ri = F, Cl, Br, I, OH, NO2, CN, CF3, CF2CF3, 1-4C alkyl, 26C alkenyl, 2-6C alkynyl, alkoxy, 3-7C cycloalkyl, carboxyl, formyl, acetyl, propanoyl, butyryl, valeryl, pivaloyl, hexanoyl, acetamido, acetate, carbamyl, carboxy, NH2, mono- or dialkylamino, phenyl, benzyl or phenethyl;

Rh = Ri or naphthyl, heterocycle or keto;

m = 2-5;

n = 0-5;

p = 0-2;

q = 1-4; and

r = 0-4.

With the Proviso that:

(i) when R1 and Het are both 2-pyridinyl, R2 and R3 are other than 4-diethylamino-2-phenyl;

(ii) when R1 is 4-carboxy-phenethyl, Het and either R2 or R3 are not both dimethylamino-thiophene;

(iii) R2 and R3 are not both H or both SCH3; and

(iv) when R2 is H and R3 is phenyl, Het is other than 2-furanyl.

ACTIVITY - Cytostatic; gynecological; antidiabetic; ophthalmological; antipsoriatic; nootropic; neuroprotective; antiparkinsonian; cerebroprotective; vasotropic; anticonvulsant; osteopathic; antiinflammatory; immunosuppressive; anti-HIV; virucide.

MECHANISM OF ACTION - Kinase inhibitor.

Tests were carried out to determine inhibition of activity of e.g.:

(a) vascular endothelial growth factor receptor-1 kinase;

(b) trkA tyrosine kinase;

(c) mixed lineage kinase-1; and

(d) fibroplast growth factor receptor kinase (FGFR).

Results for % inhibition for 4-(indol-3-ylmethylene)-3-(1,3-thiazol-2-

yl)-2 pyrazolin-5-one (1 micro M) were:
(a) 66 %;
(b) 65 %;
(c) 11 %; and
(d) 52 %.
USE - For treating or preventing angiogenic disorders, e.g. cancer of solid tumors, endometriosis, diabetic retinopathy, psoriasis, hemangioblastoma, ocular disorders or macular degeneration; also Alzheimer's disease, amyotrophic lateral sclerosis, Parkinson's disease, stroke, ischemia, Huntington's disease, AIDS dementia, epilepsy, multiple sclerosis, peripheral neuropathy, injuries of the brain or spinal chord, cancer, restenosis, osteoporosis, inflammation, viral infections, bone or hematopoietic disease, autoimmune diseases or transplant rejection. (I) can be administered with other active agents.
Dwg.0/0
FS CPI
FA AB; GI; DCN
MC CPI: B06-H; B07-D08; B14-A02; B14-C03; B14-D06; B14-F02; B14-F02D; B14-G02C; B14-G02D; B14-H01B; **B14-J01A3**; B14-J01A4; B14-J07; B14-N01; B14-N03; B14-N16; B14-S01

L34 ANSWER 3 OF 5 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
AN **2001-236883** [25] WPIX
DNN N2001-169466 DNC C2001-071244
TI New polynucleotides encoding c-Jun N-terminal kinase kinase kinases i.e. **MLK4**, PAK4, associated with skin damage for use in drug screening and development.
DC B04 D16 S03
IN BLUMENBERG, M; GAZEL, A M
PA (UYNY) UNIV NEW YORK STATE
CYC 28
PI EP 1085093 A2 20010321 (200125)* EN 51 C12N015-54
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI
CA 2318519 A1 20010320 (200130) EN C12N015-12
JP 2001157590 A 20010612 (200139) 132 C12N015-09
JP 2004290197 A 20041021 (200469) 36 C12N015-09
JP 3597124 B2 20041202 (200480) 76 C12N015-09
US 2004241739 A1 20041202 (200481) C12Q001-68
ADT EP 1085093 A2 EP 2000-307866 20000912; CA 2318519 A1 CA 2000-2318519 20000918; JP 2001157590 A JP 2000-284980 20000920; JP 2004290197 A Div ex JP 2000-284980 20000920, JP 2004-139636 20040510; JP 3597124 B2 JP 2000-284980 20000920; US 2004241739 A1 Provisional US 1999-155029P 19990920, Div ex US 2000-659737 20000911, US 2004-885921 20040707
FDT JP 3597124 B2 Previous Publ. JP 2001157590
PRAI US 1999-155029P 19990920; US 2000-659737 20000911; US 2004-885921 20040707
IC ICM C12N015-09; C12N015-12; C12N015-54; C12Q001-68
ICS C07H021-04; C07K014-47; C07K016-18; C07K016-40; C12N001-15; C12N001-19; C12N001-21; C12N005-10; C12N009-12; C12N015-63; C12N015-66; C12Q001-02; C12Q001-48; G01N033-15; **G01N033-50**; G01N033-68
AB EP 1085093 A UPAB: 20011129
NOVELTY - The human polynucleotide sequence as defined by the amino acid (aa) sequence of the:
(i) **MLK4** gene comprising 54 aa, (I);
(ii) PAK4 gene comprising 48 aa, (II);
(iii) PAK5 gene comprising 48 aa, (III), a 311 aa, (IV) or a 681 aa, (V); and the
(iv) YSK gene comprising 48 aa, (VI),
as defined in the specification are new.
DETAILED DESCRIPTION - INDEPENDENT CLAIMS are included for the following:
(1) a recombinant vector comprising (I-VI) or derivatives of (I-VI);
(2) a host cell comprising (1);
(3) a substantially purified or isolated polypeptide comprising an amino acid sequence selected from (I-VI);
(4) the preparation of (3) comprising culturing host cells of (2) under conditions that allow the expression of the polypeptide or peptide fragment and the recovery of the polypeptide or peptide fragment;
(5) an isolated antibody specific to a polypeptide comprising (I-VI);
(6) the screening for compounds that affect the cellular levels of a c-Jun N-terminal kinase kinase kinase (JNKKK) gene product;
(7) the screening for compounds that affect the activity of a JNKKK;
(8) the identification of a compound that binds to a PAK5 polypeptide comprising the sequence (III-V) or that binds to a YSK2

polypeptide comprising the sequence (VI);
(9) the screening for compounds that affect the expression of a gene that encodes a JNKKK gene product;
(10) the detection of an MLK4-, PAK4-, PAK5-, YSK2- related polynucleotide in a sample.
USE - The claimed JNKKK polynucleotide sequences of MLK4, PAK4, PAK5 or YSK2 are useful for elucidation of components involved in the cellular response to ultraviolet radiation. Methods for the isolation of antibodies specific to a polypeptide comprising (I-VI); the screening for compounds that affect the cellular levels of a c-Jun N-terminal kinase kinase kinase (JNKKK) gene product; the screening for compounds that affect the activity of a JNKKK; the identification of a compound that binds to a PAK5 polypeptide comprising the sequence (III-V) or that binds to a YSK2 polypeptide comprising the sequence (VI); the screening for compounds that affect the expression of a gene that encodes a JNKKK gene product and the detection of an MLK4-, PAK4-, PAK5-, YSK2- related polynucleotide in a sample (claimed) which allow such elucidation are outlined.
Dwg.0/3

FS CPI EPI
FA AB; DCN
MC CPI: B04-C01G; B04-E03E; B04-E06; B04-E08; B04-F01; B04-F02; B04-G03; B04-G21; B04-G22; B04-L01; B04-N02A; B11-C07A; B11-C07B2; B11-C08E; B12-K04A1; B12-K04F; D05-A02; D05-C03; D05-H08; D05-H09; D05-H11A; D05-H12A; D05-H12D1; D05-H12D2; D05-H12D4; D05-H12E; D05-H17; D05-H17A
EPI: S03-E14H

L34 ANSWER 4 OF 5 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
AN 2000-565279 [52] WPIX
DNC C2000-168346
TI Cyclic substituted fused pyrrolocarbazole and isoindolone derivatives as protein kinase inhibitors useful for treating and preventing e.g. prostate disorders, Alzheimer's disease, AIDS dementia or epilepsy.
DC B02
IN HUDKINS, R L; REDDY, D; SINGH, J; TRIPATHY, R; UNDERINER, T L; REDDY, D R; UNDERINER, T
PA (CEPH-N) CEPHALON INC
CYC 91
PI WO 2000047583 A1 20000817 (200052)* EN 131 C07D487-04
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ TZ UG ZW
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW
AU 2000033604 A 20000829 (200062)
NO 2001003887 A 20011011 (200174) C07D000-00
EP 1165562 A1 20020102 (200209) EN C07D487-04
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI
KR 2001102085 A 20011115 (200231) C07D487-04
BR 2000008056 A 20020409 (200232) C07D487-04
SK 2001001129 A3 20020404 (200232) C07D487-04
HU 2001005363 A2 20020628 (200255) C07D487-04
CN 1350537 A 20020522 (200258) C07D487-04
CZ 2001002878 A3 20020814 (200263) C07D487-04
MX 2001008114 A1 20020301 (200362) A61K031-40
ZA 2001006364 A 20030923 (200368) 149 C07D000-00
JP 2003529537 W 20031007 (200370) 145 C07D487-04
NZ 513097 A 20040528 (200437) C07D487-04
AU 773335 B2 20040520 (200462) C07D487-04
US 2004186157 A1 20040923 (200463) A61K031-407
ADT WO 2000047583 A1 WO 2000-US3476 20000211; AU 2000033604 A AU 2000-33604 20000211; NO 2001003887 A WO 2000-US3476 20000211, NO 2001-3887 20010809; EP 1165562 A1 EP 2000-911759 20000211, WO 2000-US3476 20000211; KR 2001102085 A KR 2001-710212 20010811; BR 2000008056 A BR 2000-8056 20000211, WO 2000-US3476 20000211; SK 2001001129 A3 WO 2000-US3476 20000211, SK 2001-1129 20000211; HU 2001005363 A2 WO 2000-US3476 20000211, HU 2001-5363 20000211; CN 1350537 A CN 2000-803647 20000211; CZ 2001002878 A3 WO 2000-US3476 20000211, CZ 2001-2878 20000211; MX 2001008114 A1 WO 2000-US3476 20000211, MX 2001-8114 20010810; ZA 2001006364 A ZA 2001-6364 20010802; JP 2003529537 W JP 2000-598503 20000211, WO 2000-US3476 20000211; NZ 513097 A NZ 2000-513097 20000211, WO 2000-US3476 20000211; AU 773335 B2 AU 2000-33604 20000211; US 2004186157 A1 Provisional US 1999-119834P 19990212, Cont of US 2000-500849 20000210, US 2004-755505

20040112
FDT AU 2000033604 A Based on WO 2000047583; EP 1165562 A1 Based on WO 2000047583; BR 2000008056 A Based on WO 2000047583; SK 2001001129 A3 Based on WO 2000047583; HU 2001005363 A2 Based on WO 2000047583; CZ 2001002878 A3 Based on WO 2000047583; MX 2001008114 A1 Based on WO 2000047583; JP 2003529537 W Based on WO 2000047583; NZ 513097 A Based on WO 2000047583; AU 773335 B2 Previous Publ. AU 2000033604, Based on WO 2000047583
PRAI US 2000-500849 20000210; US 1999-119834P 19990212;
US 2004-755505 20040112
IC ICM A61K031-40; A61K031-407; C07D000-00; C07D487-04
ICS A61K031-4745; A61K031-5025; A61P009-10; A61P011-00; A61P013-08; A61P015-00; A61P017-02; A61P017-06; A61P019-02; A61P025-00; A61P025-02; A61P025-08; A61P025-14; A61P025-16; A61P025-28; A61P027-02; A61P029-00; A61P031-18; A61P035-00; A61P037-06; A61P043-00; C07D209-56; C07D519-00
AB WO 200047583 A UPAB: 20011129
NOVELTY - Cyclic substituted fused pyrrolocarbazole and isoindolone derivatives (I) are new.

DETAILED DESCRIPTION - Cyclic substituted fused pyrrolocarbazole and isoindolone derivatives of formula (I) are new.

B', F' = a) an unsaturated 6-membered carbocyclic aromatic ring in which from 1 to 3 carbon atoms may be replaced by nitrogen atoms; b) an unsaturated 5-membered carbocyclic aromatic ring; and c) an unsaturated 5-membered carbocyclic aromatic ring in which either 1) one carbon atom is replaced with an oxygen, nitrogen, or sulfur atom; 2) two carbon atoms are replaced with a sulfur and a nitrogen atom, an oxygen and a nitrogen atom, or two nitrogen atoms; or 3) three carbon atoms are replaced with three nitrogen atoms;

R1 = 1-4C alkyl, aryl, arylalkyl, heteroaryl or heteroarylalkyl (all optionally substituted), H, -C(O)R9, -OR10, C(O)NH2, -NR11R12, -(CH2)pNR11R12, -(CH2)pOR10, -O(CH2)pOR10 or -O(CH2)pNR11R12;

R3-R6 = H, aryl, heteroaryl, halo, -CN, -CF3, -NO2, -OH, -OR9, -O(CH2)pNR11R12, -OC(O)R9, -OC(O)NR11R12, -O(CH2)pOR10, -CH2OR10, -NR11R12, -NR10S(O)2R9, -NR10C(O)R9, -CH2OR14, -NR10C(O)NR11R12, -CO2R2, -C(O)R2, -C(O)NR11R12, -CH=NOR2 , -CH=NR9, -(CH2)pNR11R12, -(CH2)pNHR14, -CH=NNR2R2A, -S(O)yR2, -(CH2)pS(O)yR9, -CH2S(O)yR14; or 1-8C alkyl, 2-8C alkenyl, 2-8C alkynyl (all optionally substituted with 1-3 T)

Q = O, S, NR13, NR7, CHR15, X3CH(R15), and CH(R15)X3; and

W' = CR18R7 or CHR2;

A1, B1 = H;

A2, B2 = H, OR2, SR2 or N(R2)2; or

A1 + A2, B1 + B2 = =O, =S or =NR2; provided that at least one of A1 + A2, or B1 + B2, form =O.

The full definition is given in DEFINITION (Full Definition) field.

ACTIVITY - Cytostatic; antirheumatic; antiarthritic; cerebroprotective; neuroprotective; vulnerary; antiarteriosclerotic; nootropic; antiparkinsonian; vasotropic; anticonvulsant; antiinflammatory; gynecological; antipsoriatic; ophthalmological; antidiabetic; osteopathic; virucidal; immunosuppressive. Compounds (I) have IC50 of 8-555 nM (% inhibition at 300 nM) as measured in an ELISA-based assay for determining the ability of (I) to inhibit the kinase activity of baculovirus-expressed human trkA cytoplasmic domain.

MECHANISM OF ACTION - Kinase inhibitor such as tyrosine (trkA) kinase, vascular growth factor receptor (VEGFR) **kinase**, **mixed lineage kinase (MLK)** or fibroplast growth receptor (FGFR) kinase inhibitors.

USE - (I) are useful for treating and preventing prostate disorders (e.g. prostate cancer or benign prostate hyperplasia), neoplasia, rheumatoid arthritis, pulmonary fibrosis, myelofibrosis, abnormal wound healing, atherosclerosis, Alzheimer's disease, amyotropic lateral sclerosis, Parkinson's disease, stroke, ischemia, Huntington's disease, AIDS dementia, epilepsy, multiple sclerosis, peripheral neuropathy, injuries of the brain or spinal cord, inflammation, cancer (e.g. solid tumors or a hematopoietic or lymphatic malignancy), endometriosis, psoriasis, hemangioblastoma or ocular disease (e.g. diabetic retinopathy), restenosis, osteoporosis, angiogenesis, viral infections, autoimmune diseases or transplant rejection.

Dwg.0/0
FS CPI
FA AB; GI; DCN
MC CPI: B06-D18; B14-A02; B14-C03; B14-C09; B14-D01; B14-D06; B14-F07; B14-F09; B14-G02; B14-H01; **B14-J01A3**; B14-J01A4; B14-J01B3; B14-J07; B14-N01; B14-N03; B14-N14; B14-N17C; B14-S04

L34 ANSWER 5 OF 5 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
AN **2000-282953** [24] WPIX

DNN N2000-212986 DNC C2000-085313
TI Identifying compounds that modulate **multiple lineage kinase proteins**, useful e.g. for treating neurodegeneration or cancer, from their effect on survival or death of kinase-expressing cells.
DC B04 D16 S03
IN DIONNE, C A; GLICKSMAN, M A; KNIGHT, E; MARONEY, A; NEFF, N; WALTON, K M; KHIGHT, E; DIONE, C A
PA (CEPH-N) CEPHALON INC
CYC 88
PI WO 2000013015 A1 20000309 (200024)* EN 157 G01N033-50 <--
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ UG ZW
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG UZ VN YU ZA ZW
AU 9956793 A 20000321 (200031)
NO 2001000389 A 20010402 (200131) G01N000-00
EP 1105728 A1 20010613 (200134) EN G01N033-50 <--
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI
BR 9913190 A 20011211 (200203) G01N033-50 <--
CN 1314999 A 20010926 (200206) G01N033-50 <--
HU 2001003079 A2 20011228 (200216) G01N033-50 <--
CZ 2001000701 A3 20020417 (200231) G01N033-50 <--
KR 2001103573 A 20011123 (200232) C12Q001-48
SK 2001000254 A3 20020604 (200247) G01N033-50 <--
ZA 2001000835 A 20020626 (200251) 200 G01N000-00
JP 2002523780 W 20020730 (200264) 194 G01N033-50 <--
MX 2001002020 A1 20011101 (200279) A61K031-40
AU 765637 B 20030925 (200373) G01N033-50 <--
NZ 509612 A 20031031 (200380) G01N033-50 <--
ADT WO 2000013015 A1 WO 1999-US18864 19990818; AU 9956793 A AU 1999-56793 19990818; NO 2001000389 A WO 1999-US18864 19990818, NO 2001-389 20010123; EP 1105728 A1 EP 1999-943759 19990818, WO 1999-US18864 19990818; BR 9913190 A BR 1999-13190 19990818, WO 1999-US18864 19990818; CN 1314999 A CN 1999-810135 19990818; HU 2001003079 A2 WO 1999-US18864 19990818, HU 2001-3079 19990818; CZ 2001000701 A3 WO 1999-US18864 19990818, CZ 2001-701 19990818; KR 2001103573 A KR 2001-702385 20010224; SK 2001000254 A3 WO 1999-US18864 19990818, SK 2001-254 19990818; ZA 2001000835 A ZA 2001-835 20010130; JP 2002523780 W WO 1999-US18864 19990818, JP 2000-567949 19990818; MX 2001002020 A1 MX 2001-2020 20010226; AU 765637 B AU 1999-56793 19990818; NZ 509612 A NZ 1999-509612 19990818, WO 1999-US18864 19990818
FDT AU 9956793 A Based on WO 2000013015; EP 1105728 A1 Based on WO 2000013015; BR 9913190 A Based on WO 2000013015; HU 2001003079 A2 Based on WO 2000013015; CZ 2001000701 A3 Based on WO 2000013015; SK 2001000254 A3 Based on WO 2000013015; JP 2002523780 W Based on WO 2000013015; AU 765637 B Previous Publ. AU 9956793, Based on WO 2000013015; NZ 509612 A Based on WO 2000013015
PRAI US 1998-97980P 19980826
IC ICM A61K031-40; C12Q001-48; G01N000-00; **G01N033-50**
ICS A61K031-407; A61K031-535; A61K031-5395; A61K031-55; A61P025-28; A61P029-00; C07D487-14; C07D491-22; C12N009-12; C12Q001-02; C12Q001-68; G01N033-15; **G01N033-53**; G01N033-566; G01N033-68
AB WO 200013015 A UPAB: 20021105
NOVELTY - Method for identifying compounds (A) that modulate activity of a **multiple lineage kinase protein** (I) and promotes either cell survival or cell death comprises treating a cell that contains (I) with a test compound and determining if it (i) decreases or increases the activity of (I) and (ii) promotes cell survival or death.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following: (a) method for modulating activity of (I) by treating it, or cells containing it, with a compound of formulae (II), (III) or (IV).

In (II), rings B and F = carbocyclic or heterocyclic aromatic rings; unless otherwise stated, all R groups = H or various substituents;

A1 and A2, B1 and B2 = are two H, or one H plus OR2, SR2, or N(R2)2, or together they form oxo, thioxo or =NR2;

R2 = H, 1-4C alkyl or alkoxy, hydroxy, -OCOR9, -OCONR11R12, -O(CH2)pNR11R12, -O(CH2)pOR10, 6-10C aralkyl or heteroarylalkyl (both optionally substituted);

R9 = alkyl, aryl or heteroaryl;

R10 = hydrogen or 1-4C alkyl;

R11 and R12 = R10 or together complete (thio)morpholino or piperidino;

p = 1-4;
m and n = 0-2;
Y = O, S, NR10, N(O-)R10, N(OR10) or methylene;
Z' = bond, oxygen, vinylene, sulfur, carbonyl, CH(OR10), NR10, CH(NR11R12), CONR17, N(R17)CO, N(S(O)yR9), N(S(O)yNR11R12), NCOR17, CR15R16, N+(O-)R10, CH(OH)CH(OH) or CH(OCOR9)CH(OCOR9);
y = 0-2;
R17 = H or R9;
R15, R16 = H, OH, COR10, OCOR9, hydroxyalkyl or COOR10;
in (III), Z1 and Z2 = H or together are oxo;
R1, R2 and X = H or various substituents;
R = hydroxy or methoxy;
in (IV), Z1 and Z2 = H or together are oxo;
R1 = H or Br;
R3 = H, allyl, 3-hydroxypropyl or 3-morpholino-propyl;
R4 = as R3 but not morpholinopropyl.
The full definitions are given in the DEFINITIONS (Full Definitions) Field;
(b) method for identifying a compound (A') for treatment of neurodegeneration or inflammation from its ability to decrease activity of (I); and
(c) method for treating neurodegeneration or inflammation by administering (A').
ACTIVITY - Anti-neurodegenerative; antiinflammatory; anticancer.
MECHANISM OF ACTION - **Multiple lineage kinase** modulators .
USE - (A) are potentially useful for treatment of neurodegenerative diseases (e.g. Alzheimer's, Huntington's and Parkinson's diseases, amyotrophic lateral sclerosis, ischemia etc.), also (not claimed) malignant cell growth.
Dwg.0/23
FS CPI EPI
FA AB; GI; DCN
MC CPI: B05-B01E; B06-H; **B11-C08E2**; B12-K04; B14-C03; B14-D06; B14-F02D; B14-H01B; **B14-J01**; **D05-H09**
EPI: S03-E14H

=> b medl
FILE 'MEDLINE' ENTERED AT 15:03:51 ON 11 JAN 2005

FILE LAST UPDATED: 8 JAN 2005 (20050108/UP). FILE COVERS 1950 TO DATE.

On December 19, 2004, the 2005 MeSH terms were loaded.

Warning: The search L-number/HUMAN limit is missing from records indexed with the new 2005 MeSH (records added since December 19, 2004). Until this is corrected, include HUMANS/CT and 20041219-20051231/ED in searches to limit results to humans for this time period.

OLDMEDLINE now back to 1950.

MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the MeSH 2005 vocabulary. See http://www.nlm.nih.gov/mesh/ and http://www.nlm.nih.gov/pubs/techbull/nd03/nd03_mesh.html for a description of changes.

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> d all l38

L38 ANSWER 1 OF 1 MEDLINE on STN
AN 2004043739 MEDLINE
DN PubMed ID: 14744254
TI **Mixed-lineage kinases**: a target for the prevention of neurodegeneration.
AU Wang Leo H; Besirli Cagri G; Johnson Eugene M Jr
CS Departments of Neurology and Molecular Biology & Pharmacology, Washington University School of Medicine, Saint Louis, Missouri 63110-1031, USA.
SO Annual review of pharmacology and toxicology, (2004) 44 451-74. Ref: 94
Journal code: 7607088. ISSN: 0362-1642.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)

LA English
FS Priority Journals
EM 200405
ED Entered STN: 20040128
Last Updated on STN: 20040514
Entered Medline: 20040513
AB The activation of the c-Jun N-terminal kinase (JNK) pathway is critical for naturally occurring neuronal cell death during development and may be important for the pathological neuronal cell death of neurodegenerative diseases. The small molecule inhibitor of the **mixed-lineage kinase (MLK)** family of kinases, CEP-1347, inhibits the activation of the JNK pathway and, consequently, the cell death in many cell culture and animal models of neuronal death. CEP-1347 has the ability not only to inhibit cell death but also to maintain the trophic status of neurons in culture. The possible importance of the JNK pathway in neurodegenerative diseases such as Alzheimer's and Parkinson's diseases provides a rationale for the use of CEP-1347 for the treatment of these diseases. CEP-1347 has the potential of not only retarding disease progression but also reversing the severity of symptoms by improving the function of surviving neurons.
CT Check Tags: Human
Alzheimer Disease: EN, enzymology
Alzheimer Disease: PP, physiopathology
Alzheimer Disease: PC, prevention & control
Animals
Carbazoles: PD, pharmacology
Hearing Loss: PP, physiopathology
Indoles: PD, pharmacology
MAP Kinase Kinase Kinases: AI, antagonists & inhibitors
*MAP Kinase Kinase Kinases: ME, metabolism
Mitogen-Activated Protein Kinases: AI, antagonists & inhibitors
Mitogen-Activated Protein Kinases: ME, metabolism
Models, Biological
Neurodegenerative Diseases: DT, drug therapy
*Neurodegenerative Diseases: EN, enzymology
*Neurodegenerative Diseases: PC, prevention & control
Neuroprotective Agents: PD, pharmacology
Parkinson Disease: EN, enzymology
Parkinson Disease: PP, physiopathology
Parkinson Disease: PC, prevention & control
RN 97161-97-2 (K 252)
CN 0 (CEP 1347); 0 (Carbazoles); 0 (Indoles); 0 (Neuroprotective Agents); EC 2.7.1.37 (MAP Kinase Kinase Kinases); EC 2.7.1.37 (Mitogen-Activated Protein Kinases); EC 2.7.10.- (JNK mitogen-activated protein kinases)

=> b embase
FILE 'EMBASE' ENTERED AT 15:04:00 ON 11 JAN 2005

FILE COVERS 1974 TO 6 Jan 2005 (20050106/ED)

EMBASE has been reloaded. Enter HELP RLOAD for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> d all l52 tot

L52 ANSWER 1 OF 2 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
AN 2004032794 EMBASE
TI Kainate Receptor Activation Induces **Mixed Lineage Kinase**-mediated Cellular Signaling Cascades via Post-synaptic Density Protein 95.
AU Savinainen A.; Garcia E.P.; Dorow D.; Marshall J.; **Liu Y.F.**
CS Y.F. Liu, Northeastern University, 312 Mugar Hall, 360 Huntington Ave., Boston, MA 02115, United States. yafliu@lynx.neu.edu
SO Journal of Biological Chemistry, (6 Apr 2001) 276/14 (11382-11386). Refs: 29
ISSN: 0021-9258 CODEN: JBCHA3
CY United States
DT Journal; Article
FS 029 Clinical Biochemistry
LA English
SL English

AB Kainate receptor glutamate receptor 6 (GluR6) subunit-deficient and c-Jun N-terminal kinase 3 (JNK3)-null mice share similar phenotypes including resistance to kainite-induced epileptic seizures and neuronal toxicity (Yang, D. D., Kuan, C.-Y., Whitmarsh, A. J., Rincon, M., Zheng, T. S., Davis, R. J., Rakis, P., and Flavell, R. (1997) Nature 389, 865-869; Mulle, C., Seiler, A., Perez-Otano, I., Dickinson-Anson, H., Castillo, P. E., Bureau, I., Maron, C., Gage, F. H., Mann, J. R., Bettler, B., and Heinemmann, S. F. (1998) Nature 392, 601-605). This suggests that JNK activation may be involved in GluR6-mediated excitotoxicity. We provide evidence that postsynaptic density protein (PSD-95) links GluR6 to JNK activation by anchoring **mixed lineage kinase** (**MLK**) 2 or **MLK3**, upstream activators of JNKs, to the receptor complex. Association of **MLK2** and **MLK3** with PSD-95 in HN33 cells and rat brain preparations is dependent upon the SH3 domain of PSD-95, and expression of GluR6 in HN33 cells activated JNKs and induced neuronal apoptosis. Deletion of the PSD-95-binding site of GluR6 reduced both JNK activation and neuronal toxicity. Co-expression of dominant negative **MLK2**, **MLK3**, or mitogen-activated kinase kinase (MKK) 4 and MKK7 also significantly attenuated JNK activation and neuronal toxicity mediated by GluR6, and co-expression of PSD-95 with a deficient Src homology 3 domain also inhibited GluR6-induced JNK activation and neuronal toxicity. Our results suggest that PSD-95 plays a critical role in GluR6-mediated JNK activation and excitotoxicity by anchoring **MLK** to the receptor complex.

CT Medical Descriptors:
*signal transduction
cell lineage
enzyme activation
cytotoxicity
protein binding
nerve cell necrosis
apoptosis
Src homology domain
nonhuman
rat
controlled study
animal cell
article
priority journal
Drug Descriptors:
*kainic acid receptor
*postsynaptic density protein 95
*phosphotransferase
***mixed lineage kinase**
stress activated protein kinase
glutamate receptor
unclassified drug

RN (phosphotransferase) 9031-09-8, 9031-44-1; (stress activated protein kinase) 155215-87-5

L52 ANSWER 2 OF 2 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

AN 2004032719 EMBASE

TI Activated JNK Phosphorylates the C-terminal Domain of **MLK2** That is Required for **MLK2**-induced Apoptosis.

AU Phelan D.R.; Price G.; **Liu Y.F.**; Dorow D.S.

CS D.S. Dorow, Trescowthick Research Centre, Peter MacCallum Cancer Institute, Locked Bag #1 A'Beckett St., Melbourne, Vic. 8006, Australia. d.dorow@pmci.unimelb.edu.au

SO Journal of Biological Chemistry, (6 Apr 2001) 276/14 (10801-10810). Refs: 51
ISSN: 0021-9258 CODEN: JBCHA3

CY United States

DT Journal; Article

FS 029 Clinical Biochemistry

LA English

SL English

AB MAP kinase signaling pathways are important mediators of cellular responses to a wide variety of stimuli. Signals pass along these pathways via kinase cascades in which three protein kinases are sequentially phosphorylated and activated, initiating a range of cellular programs including cellular proliferation, immune and inflammatory responses, and apoptosis. One such cascade involves the **mixed lineage kinase**, **MLK2**, signaling through MAP kinase kinase 4 and/or MAP kinase kinase 7 to the SAPK/JNK, resulting in phosphorylation of transcription factors including the oncogene, c-jun. Recently we showed

that **MLK2** causes apoptosis in cultured neuronal cells and that this effect is dependent on activation of the JNK pathway (Liu, Y. F., Dorow, D. S., and Marshall, J. (2000) J. Biol. Chemical 275, 19035-19040). Furthermore, dominant-negative **MLK2** blocked apoptosis induced by polyglutamine-expanded huntingtin protein, the product of the mutant Huntington's disease gene. Here we show that as well as activating the stress-signaling pathway, **MLK2** is a target for phosphorylation by activated JNK. Phosphopeptide mapping of **MLK2** proteins revealed that activated JNK2 phosphorylates multiple sites mainly within the noncatalytic C-terminal region of **MLK2** including the C-terminal 100 amino acid peptide. In addition, **MLK2** is phosphorylated in vivo within several of the same C-terminal peptides phosphorylated by JNK2 in vitro, and this phosphorylation is increased by cotransfection of JNK2 and treatment with the JNK activator, anisomycin. Cotransfection of dominant-negative JNK kinase inhibits phosphorylation of kinase-negative **MLK2** by anisomycin-activated JNK. Furthermore, we show that the N-terminal region of **MLK2** is sufficient to activate JNK but that removal of the C-terminal domain abrogates the apoptotic response. Taken together, these data indicate that the apoptotic activity of **MLK2** is dependent on the C-terminal domain that is the main target for **MLK2** phosphorylation by activated JNK.

CT Medical Descriptors:
*enzyme phosphorylation
***apoptosis**
signal transduction
cell proliferation
immunity
inflammation
nerve cell
protein phosphorylation
Huntington chorea
carboxy terminal sequence
nonhuman
controlled study
animal cell
article
priority journal
Drug Descriptors:
*Janus kinase
*phosphotransferase
***mixed lineage kinase 2**
***MLK2 protein**
mitogen activated protein kinase
mitogen activated protein kinase kinase
transcription factor
huntingtin
polyglutamine
phosphopeptide
amino acid
anisomycin
unclassified drug

RN (Janus kinase) 161384-16-3; (phosphotransferase) 9031-09-8, 9031-44-1; (mitogen activated protein kinase) 142243-02-5; (mitogen activated protein kinase kinase) 142805-58-1; (huntingtin) 191683-04-2; (polyglutamine) 26700-71-0, 69864-43-3; (amino acid) 65072-01-7; (anisomycin) 22862-76-6

=> d all l58 tot

L58 ANSWER 1 OF 6 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED.
on STN
AN **2004176740** EMBASE
TI CEP-1347.
AU Mealy N.E.; Bayes M.
CS N.E. Mealy, Prous Science, P.O. Box 540, 08080 Barcelona, Spain
SO Drugs of the Future, (2004) 29/3 (267).
Refs: 1
ISSN: 0377-8282 CODEN: DRFUD4
CY Spain
DT Journal; (Short Survey)
FS 008 Neurology and Neurosurgery
030 Pharmacology
037 Drug Literature Index
LA English
CT Medical Descriptors:
***Parkinson disease: DT, drug therapy**

nerve cell
cell survival
enzyme inhibition
human
clinical trial
short survey
Drug Descriptors:
*cep 1347: CT, clinical trial
*cep 1347: DT, drug therapy
*cep 1347: PD, pharmacology
mixed lineage kinase: EC, endogenous compound
phosphotransferase: EC, endogenous compound
dopamine: EC, endogenous compound
unclassified drug
RN (cep 1347) 156177-65-0, 170587-65-2; (phosphotransferase) 9031-09-8, 9031-44-1; (dopamine) 51-61-6, 62-31-7
CN (1) Cep 1347; (2) Cep 1347; Kt 7515
CO (1) Lundbeck; (2) Cephalon; Kyowa Hakko Kogyo

L58 ANSWER 2 OF 6 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED.
on STN
AN **2004059745** EMBASE
TI The safety and tolerability of a **mixed lineage kinase** inhibitor (CEP-1347) in PD.
AU Schwid S.R.
CS Dr. S.R. Schwid, Department of Neurology, Univ. of Rochester Medical Center, Box 605, 601 Elmwood Ave., Rochester, NY 14642, United States. steven_schwid@urmc.rochester.edu
SO Neurology, (27 Jan 2004) 62/2 (330-332).
Refs: 8
ISSN: 0028-3878 CODEN: NEURAI
CY United States
DT Journal; Article
FS 008 Neurology and Neurosurgery
037 Drug Literature Index
038 Adverse Reactions Titles
LA English
SL English
AB CEP-1347 is an inhibitor of members of the **mixed lineage kinase** family, key signals triggering apoptotic neuronal death. The authors performed a randomized, blinded, placebo-controlled study assessing the safety, tolerability, pharmacokinetics, and acute symptomatic effects of CEP-1347 in 30 patients with Parkinson's disease (PD). In this short-term study, CEP-1347 was safe and well tolerated. It had no acute effect on parkinsonian symptoms or levodopa pharmacokinetics, making it well suited for larger and longer studies of its potential to modify the course of PD.
CT Medical Descriptors:
***Parkinson disease: DT, drug therapy**
drug safety
drug tolerability
apoptosis
nerve cell necrosis
signal transduction
parkinsonism
diarrhea: SI, side effect
headache: SI, side effect
nausea: SI, side effect
vomiting: SI, side effect
human
clinical article
clinical trial
randomized controlled trial
double blind procedure
multicenter study
controlled study
aged
adult
article
priority journal
Drug Descriptors:
*cep 1347: AE, adverse drug reaction
*cep 1347: CT, clinical trial
*cep 1347: DO, drug dose
*cep 1347: DT, drug therapy
*cep 1347: PK, pharmacokinetics

*cep 1347: PD, pharmacology
*cep 1347: PO, oral drug administration
placebo
levodopa: DT, drug therapy
RN (cep 1347) 156177-65-0, 170587-65-2; (levodopa) 59-92-7
CN Cep 1347

L58 ANSWER 3 OF 6 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
AN **2004053404** EMBASE
TI Improvement of embryonic dopaminergic neurone survival in culture and after grafting into the striatum of hemiparkinsonian rats by CEP-1347.
AU Boll J.B.; Geist M.A.; Kaminski Schierle G.S.; Petersen K.; Leist M.; Vaudano E.
CS J.B. Boll, H. Lundbeck A/S, Dept. of Molecular Disease Biology, Ottiliavej 9, 2500 Valby, Denmark. jbbo@lundbeck.com
SO Journal of Neurochemistry, (2004) 88/3 (698-707).
Refs: 49
ISSN: 0022-3042 CODEN: JONRA
CY United Kingdom
DT Journal; Article
FS 008 Neurology and Neurosurgery
037 Drug Literature Index
LA English
SL English
AB Transplantation of embryonic nigral tissue ameliorates functional deficiencies in Parkinson's disease (PD). A main constraint of neural grafting is the poor survival of dopaminergic neurones grafted into patients. Studies in rats indicated that many grafted neurones die by apoptosis. CEP-1347 is a **mixed-lineage-kinase** (**MLK**) inhibitor with neuroprotective action in several in vitro and in vivo models of neuronal apoptosis. We studied the effect of CEP-1347 on the survival of embryonic rat dopaminergic neurones in culture, and after transplantation in hemiparkinsonian rats. CEP-1347 and the alternative **MLK** inhibitor CEP-11004 significantly increased the survival of dopaminergic neurones in primary cultures from rat ventral mesencephalon and in Mn (2+)-exposed PC12 cells, a surrogate model of dopaminergic lethal stress. Moreover, combined treatment of the grafting cell suspension and the host animal with CEP-1347 significantly improved the long-term survival of rat dopaminergic neurones transplanted into the striatum of hemiparkinsonian rats. Also, the protective effect of CEP-1347 resulted in an increase in total graft size and in enhanced fibre outgrowth. Thus, treatment with CEP-1347 improved dopaminergic cell survival under severe stress and might be useful to improve the positive outcome of transplantation therapy in PD and reduce the amount of human tissue required.
CT Medical Descriptors:
*dopamine release
*nerve cell
***cell survival**
*corpus striatum
***parkinsonism**
embryo cell
tissue transplantation
substantia nigra
nerve graft
dopaminergic nerve cell
statistical significance
mesencephalon
stress
cell suspension
survival time
disease severity
outcomes research
tissue specificity
nonhuman
rat
animal experiment
animal model
controlled study
animal cell
article
priority journal
Drug Descriptors:
*enzyme inhibitor: DV, drug development
*enzyme inhibitor: PD, pharmacology

***mixed lineage kinase inhibitor: DV, drug development**
***mixed lineage kinase inhibitor: PD, pharmacology**
*cep 1347: DV, drug development
*cep 1347: PD, pharmacology
neuroprotective agent: DV, drug development
neuroprotective agent: PD, pharmacology
stress activated protein kinase inhibitor: PD, pharmacology
anthra[1,9 cd]pyrazol 6(2h) one: PD, pharmacology
cep 11004: PD, pharmacology
unclassified drug
RN (cep 1347) 156177-65-0, 170587-65-2; (anthra[1,9 cd]pyrazol 6(2h) one) 129-56-6
CN (1) Cep 1347; (2) Cep 11004; (3) Sp 600125
CO (2) Cephalon (United States); (3) Calbiochem (Denmark)

L58 ANSWER 4 OF 6 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
AN **2004030867** EMBASE
TI CEP11004, a novel inhibitor of the **mixed lineage kinases**, suppresses apoptotic death in dopamine neurons of the substantia nigra induced by 6-hydroxydopamine.
AU Ganguly A.; Oo T.F.; Rzhetskaya M.; Pratt R.; Yarygina O.; Momoi T.; Kholodilov N.; Burke R.E.
CS R.E. Burke, Department of Neurology, Black Building, Columbia University, 650 West 168th Street, New York, NY 10032, United States. rb43@columbia.edu
SO Journal of Neurochemistry, (2004) 88/2 (469-480).
Refs: 54
ISSN: 0022-3042 CODEN: JONRA
CY United Kingdom
DT Journal; Article
FS 005 General Pathology and Pathological Anatomy
008 Neurology and Neurosurgery
030 Pharmacology
037 Drug Literature Index
LA English
SL English
AB There is much evidence that the kinase cascade which leads to the phosphorylation of c-jun plays an important signaling role in the mediation of programmed cell death. We have previously shown that c-jun is phosphorylated in a model of induced apoptotic death in dopamine neurons of the substantia nigra in vivo. To determine the generality and functional significance of this response, we have examined c-jun phosphorylation and the effect on cell death of a novel **mixed lineage kinase** inhibitor, CEP11004, in the 6-hydroxydopamine model of induced apoptotic death in dopamine neurons. We found that expression of total c-jun and Ser73-phosphorylated c-jun is increased in this model and both colocalize with apoptotic morphology. CEP11004 suppresses apoptotic death to levels of 44 and 58% of control values at doses of 1.0 and 3.0 mg/kg, respectively. It also suppresses, to approximately equal levels, the number of profiles positive for the activated form of capase 9. CEP11004 markedly suppresses striatal dopaminergic fiber loss in these models, to only 22% of control levels. We conclude that c-jun phosphorylation is a general feature of apoptosis in living dopamine neurons and that the **mixed lineage kinases** play a functional role as up-stream mediators of cell death in these neurons.
CT Medical Descriptors:
***apoptosis**
*dopaminergic nerve cell
*substantia nigra
signal transduction
enzyme phosphorylation
protein expression
protein localization
cell structure
dose response
enzyme activation
Parkinson disease
immunohistochemistry
Northern blotting
sequence homology
nonhuman
rat
animal model
controlled study

animal tissue
article
nucleotide sequence
priority journal
Drug Descriptors:
*cep 11004: DO, drug dose
*cep 11004: PD, pharmacology
*cep 11004: SC, subcutaneous drug administration
*enzyme inhibitor: DO, drug dose
*enzyme inhibitor: PD, pharmacology
*enzyme inhibitor: SC, subcutaneous drug administration
*oxidopamine
stress activated protein kinase
caspase 9
unclassified drug
RN (oxidopamine) 1199-18-4, 28094-15-7, 636-00-0; (stress activated protein kinase) 155215-87-5; (caspase 9) 180189-96-2
GEN GENBANK AY240864 referred number; GENBANK AY240865 referred number; GENBANK AY240866 referred number; GENBANK AY240867 referred number; GENBANK AY240868 referred number

L58 ANSWER 5 OF 6 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
AN 2002211955 EMBASE
TI **Mixed Lineage Kinase** family, potential targets for preventing neurodegeneration.
AU Maroney A.C.; Saporito M.S.; Hudkins R.L.
CS A.C. Maroney, Cephalon Inc., 145 Brandywine Pkwy., West Chester, PA 19380, United States. AMARONEY@CEPHALON.COM
SO Current Medicinal Chemistry - Central Nervous System Agents, (2002) 2/2 (143-155).
Refs: 95
ISSN: 1568-0150 CODEN: CMCCCO
CY Netherlands
DT Journal; Article
FS 008 Neurology and Neurosurgery
029 Clinical Biochemistry
030 Pharmacology
037 Drug Literature Index
LA English
SL English
AB The c-Jun amino terminal kinase (JNK) cascade leading to c-Jun phosphorylation has been implicated in the neuronal cellular response to a variety of external stimuli including free radical oxidative stress, trophic withdrawal, amyloid toxicity and activation by death domain receptor ligands. Although the exact causes of neuronal loss in neurodegenerative diseases remain unknown, it has been hypothesized that response to these environmental stresses may be contributing factors. Agents which block the JNK signaling cascade have been proposed as a therapeutic approach for preventing neuronal cell death observed in a variety of neurodegenerative diseases including Parkinson's, Huntington's, and Alzheimer's disease. The JNKs are regulated through a sequential signaling cascade by a series of upstream kinases including the **mixed lineage kinases (MLKs)**.
Herein, we review the **MLK** family as a therapeutic target and provide evidence with CEP-1347, the most advanced **MLK** inhibitor currently in clinical trails for Parkinson's disease, that intervention at the **MLK** point in the JNK cascade may reduce the susceptibility of neurons to degenerate.
CT Medical Descriptors:
***Parkinson disease: DT, drug therapy**
***Parkinson disease: ET, etiology**
***Parkinson disease: PC, prevention**
neurologic disease: DT, drug therapy
neurologic disease: ET, etiology
neurologic disease: PC, prevention
degenerative disease: DT, drug therapy
degenerative disease: ET, etiology
degenerative disease: PC, prevention
microtubule assembly
enzyme activity
enzyme phosphorylation
gene overexpression
apoptosis
nerve cell necrosis
chemical structure

enzyme inhibition
dopaminergic system
dimerization
structure activity relation
human
nonhuman
clinical trial
animal model
controlled study
animal cell
article
Drug Descriptors:
*stress activated protein kinase
*stress activated protein kinase inhibitor: CT, clinical trial
*stress activated protein kinase inhibitor: AD, drug administration
*stress activated protein kinase inhibitor: AN, drug analysis
*stress activated protein kinase inhibitor: DV, drug development
*stress activated protein kinase inhibitor: DO, drug dose
*stress activated protein kinase inhibitor: DT, drug therapy
*stress activated protein kinase inhibitor: PD, pharmacology
*stress activated protein kinase inhibitor: SC, subcutaneous drug administration
***mixed lineage kinase inhibitor: CT, clinical trial**
***mixed lineage kinase inhibitor: AD, drug administration**
***mixed lineage kinase inhibitor: AN, drug analysis**
***mixed lineage kinase inhibitor: DV, drug development**
***mixed lineage kinase inhibitor: DO, drug dose**
***mixed lineage kinase inhibitor: DT, drug therapy**
***mixed lineage kinase inhibitor: PD, pharmacology**
***mixed lineage kinase inhibitor: SC, subcutaneous drug administration**
*cep 1347: CT, clinical trial
*cep 1347: AD, drug administration
*cep 1347: AN, drug analysis
*cep 1347: DV, drug development
*cep 1347: DO, drug dose
*cep 1347: DT, drug therapy
*cep 1347: PD, pharmacology
*cep 1347: SC, subcutaneous drug administration
*k 252a: AN, drug analysis
*k 252a: DV, drug development
*k 252a: PD, pharmacology
*antiparkinson agent: CT, clinical trial
*antiparkinson agent: AD, drug administration
*antiparkinson agent: AN, drug analysis
*antiparkinson agent: DV, drug development
*antiparkinson agent: DO, drug dose
*antiparkinson agent: DT, drug therapy
*antiparkinson agent: PD, pharmacology
*antiparkinson agent: SC, subcutaneous drug administration
mitogen activated protein kinase
proline
neurotoxin: TO, drug toxicity
1,2,3,6 tetrahydro 1 methyl 4 phenylpyridine: TO, drug toxicity
unclassified drug

RN (stress activated protein kinase) 155215-87-5; (cep 1347) 156177-65-0, 170587-65-2; (k 252a) 97161-97-2; (mitogen activated protein kinase) 142243-02-5; (proline) 147-85-3, 7005-20-1; (neurotoxin) 39386-17-9; (1,2,3,6 tetrahydro 1 methyl 4 phenylpyridine) 28289-54-5
CN Cep 1347

L58 ANSWER 6 OF 6 EMBASE
on STN
AN **97065523** EMBASE
DN 1997065523
TI MEKKs, GCKs, **MLKs**, PAKs, TAKs, and Tpls: Upstream regulators of the c-Jun amino-terminal kinases?.
AU Fanger G.R.; Gerwins P.; Widmann C.; Jarpe M.B.; Johnson G.L.
CS G.L. Johnson, Division of Basic Sciences, National Jewish Center, Immunology and Respiratory Medicine, 1400 Jackson Street, Denver, CO 80206, United States. johnsong@njc.org
SO Current Opinion in Genetics and Development, (1997) 7/1 (67-74).
Refs: 58
ISSN: 0959-437X CODEN: COGDET
CY United Kingdom
DT Journal; Article

FS 021 Developmental Biology and Teratology
022 Human Genetics
LA English
SL English
AB Regulation of the mitogen-activated protein kinase (MAPK) family members - which include the extracellular response kinases (ERKs), p38/HOG1, and the c-Jun amino-terminal kinases (JNKs) - plays a central role in mediating the effects of diverse stimuli encompassing cytokines, hormones, growth factors and stresses such as osmotic imbalance, heat shock, inhibition of protein synthesis and irradiation. A rapidly increasing number of kinases that activate the JNK pathways has been described recently, including the MAPK/ERK kinase kinases, p21-activated kinases, germinal center **kinase, mixed lineage kinases**, tumor progression locus 2, and TGF-.beta.-activated kinase. Thus, regulation of the JNK pathway provides an interesting example of how many different stimuli can converge into regulating pathways critical for the determination of cell fate.
CT Medical Descriptors:
*oncogene c jun
amino terminal sequence
apoptosis
article
cell differentiation
cell growth
developmental genetics
enzyme regulation
gene locus
germinal center
nonhuman
priority journal
tumor growth
Drug Descriptors:
*mitogen activated protein kinase: EC, endogenous compound
*phosphotransferase: EC, endogenous compound
*protein p21: EC, endogenous compound
*transforming growth factor beta: EC, endogenous compound
cytokine: EC, endogenous compound
growth factor: EC, endogenous compound
hormone: EC, endogenous compound
RN (mitogen activated protein kinase) 142243-02-5; (phosphotransferase) 9031-09-8, 9031-44-1; (protein p21) 85306-28-1

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